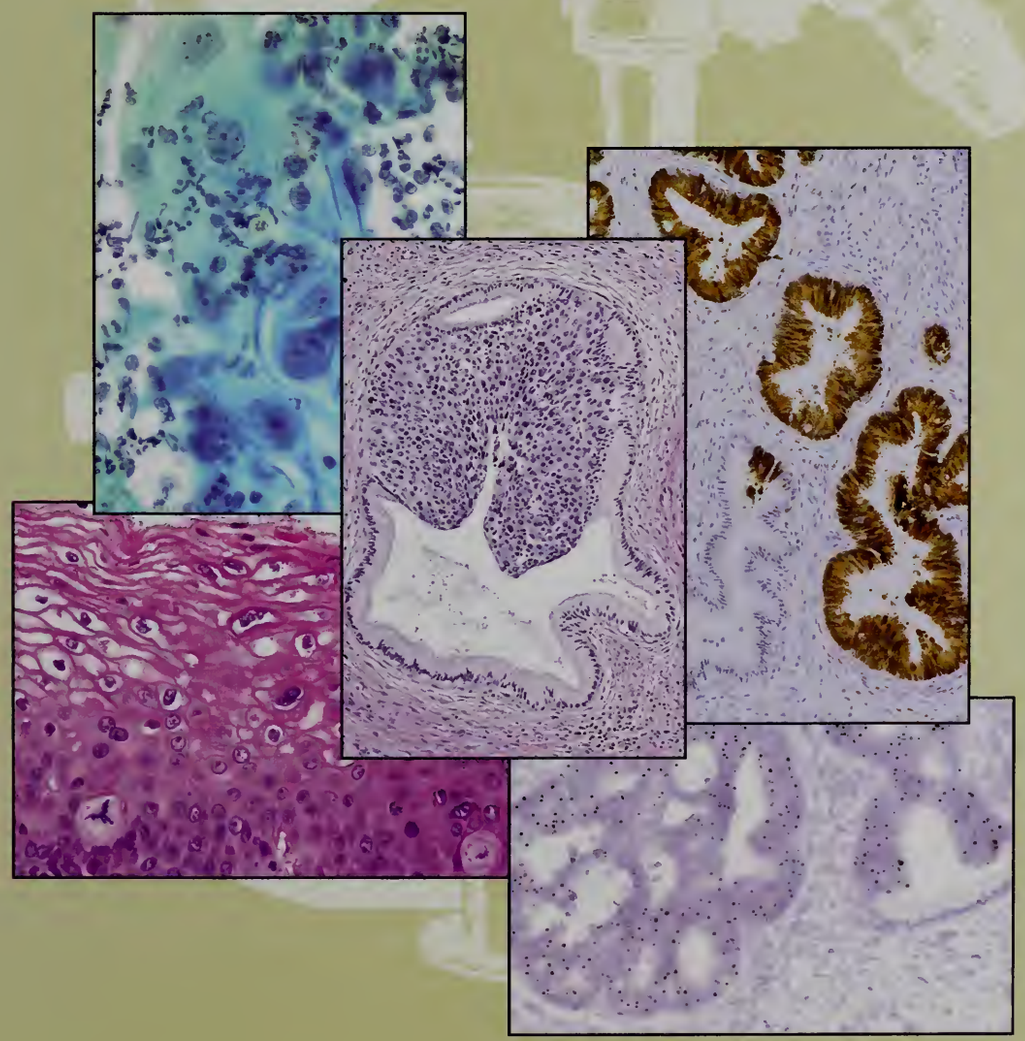
13

AFIP ATLAS OF TUMOR PATHOLOGY
Series 4

Tumors of the Cervix, Vagina, and Vulva

Robert J. Kurman, MD
Brigitte M. Ronnett, MD
Mark E. Sherman, MD
Edward J. Wilkinson, MD



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AFIP ATLAS OF TUMOR PATHOLOGY

Fourth Series
Fascicle 13

TUMORS OF THE CERVIX, VAGINA, AND VULVA

by

Robert J. Kurman, MD
Johns Hopkins University School of Medicine
Departments of Gynecology-Obstetrics and Pathology
Professor and Director, Gynecologic Pathology
Baltimore, Maryland

Brigitte M. Ronnett, MD
Johns Hopkins Univesity School of Medicine
Department of Pathology
Professor, Gynecologic Pathology
Baltimore, Maryland

Mark E. Sherman, MD
National Cancer Institute
Hormone and Reproductive Epidemiology Branch
Rockville, Maryland

Edward J. Wilkinson, MD
Univesity of Florida Medical Center
Department of Pathology
Gainesville, Florida

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University of Maryland School of Medicine
Baltimore, Maryland

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EDITORS' NOTE

The Atlas of Tumor Pathology has a long and distinguished history. It was first conceived at a cancer research meeting held in St. Louis in September 1947 as an attempt to standardize the nomenclature of neoplastic diseases. The first series was sponsored by the National Academy of Sciences-National Research Council. The organization of this Sisyphean effort was entrusted to the Subcommittee on Oncology of the Committee on Pathology, and Dr. Arthur Purdy Stout was the first editor-in-chief. Many of the illustrations were provided by the Medical Illustration Service of the Armed Forces Institute of Pathology (AFIP), the type was set by the Government Printing Office, and the final printing was done at the Armed Forces Institute of Pathology (hence the colloquial appellation "AFIP Fascicles"). The American Registry of Pathology (ARP) purchased the Fascicles from the Government Printing Office and sold them virtually at cost. Over a period of 20 years, approximately 15,000 copies each of nearly 40 Fascicles were produced. The worldwide impact of these publications over the years has largely surpassed the original goal. They quickly became among the most influential publications on tumor pathology, primarily because of their overall high quality, but also because their low cost made them easily accessible the world over to pathologists and other students of oncology.

Upon completion of the first series, the National Academy of Sciences-National Research Council handed further pursuit of the project over to the newly created Universities Associated for Research and Education in Pathology (UAREP). A second series was started, generously supported by grants from the AFIP, the National Cancer Institute, and the American Cancer Society. Dr. Harlan I. Firminger became the editor-in-chief and was succeeded by Dr. William H. Hartmann. The second series' Fascicles were produced as bound volumes instead of loose leaflets. They featured a more comprehensive coverage of the subjects, to the extent that the Fascicles could no longer be regarded as "atlases" but rather as monographs describing and illustrating in detail the tumors and tumor-like conditions of the various organs and systems.

Once the second series was completed, with a success that matched that of the first, ARP, UAREP, and AFIP decided to embark on a third series. Dr. Juan Rosai was appointed as editor-in-chief, and Dr. Leslie H. Sobin became associate editor. A distinguished Editorial Advisory Board was also convened, and these outstanding pathologists and educators played a major role in the success of this series, the first publication of which appeared in 1991 and the last (number 32) in 2003.

The same organizational framework applies to the current fourth series, but with UAREP no longer in existence, ARP plays the major role. New features include a hardbound cover, illustrations almost exclusively in color, and an accompanying electronic version of each Fascicle. There is also an increased emphasis (wherever appropriate) on the cytopathologic (intraoperative, exfoliative, and/or fine needle

aspiration) and molecular features that are important in diagnosis and prognosis. What does not change from the three previous series, however, is the goal of providing the practicing pathologist with thorough, concise, and up-to-date information on the nomenclature and classification; epidemiologic, clinical, and pathogenetic features; and, most importantly, guidance in the diagnosis of the tumors and tumorlike lesions of all major organ systems and body sites.

As in the third series, a continuous attempt is made to correlate, whenever possible, the nomenclature used in the Fascicles with that proposed by the World Health Organization's Classification of Tumors, as well as to ensure a consistency of style throughout. Close cooperation between the various authors and their respective liaisons from the Editorial Board will continue to be emphasized in order to minimize unnecessary repetition and discrepancies in the text and illustrations.

Particular thanks are due to the members of the Editorial Advisory Board, the reviewers (at least two for each Fascicle), the editorial and production staff, and—first and foremost—the individual Fascicle authors for their ongoing efforts to ensure that this series is a worthy successor to the previous three.

Steven G. Silverberg, MD
William A. Gardner, MD
Leslie H. Sobin, MD

PREFACE AND ACKNOWLEDGEMENTS

The advances in the field of cervical, vaginal, and vulvar pathology since the publication of the last edition of this Fascicle in 1992 have been remarkable, and the progress that two of the authors (Robert Kurman and Edward Wilkinson) have witnessed since they were first introduced to the field in the1970s has been stunning. At that time, the consensus was that herpesvirus type 2 caused cervical cancer and the nomenclature for cervical cancer precursors was cervical dysplasia and carcinoma in situ (CIS), with the emphasis placed on distinguishing severe dysplasia from CIS. Since then, we have learned that high-risk human papillomaviruses (HPVs) represent the etiologic agents that cause essentially all cervical and vaginal cancers, their precursors, and a substantial fraction of vulvar neoplastic lesions. The convincing efficacy of the recently developed prophylactic vaccines in preventing HPV infections and cervical cancer precursors based on cytologic and morphologic diagnosis provides undeniable evidence of the early causal role of the virus in the pathogenesis of cervical neoplasia. Examination of the trajectory of this extraordinary achievement highlights the significant contributions made by a number of disciplines, including molecular biology, epidemiology, and pathology. Undoubtedly, molecular biology has played the preeminent role with the identification by Professor Harald zur Hausen in 1977 of HPV 16 DNA in cervical cancer specimens. The award of the Nobel Prize in Medicine to Professor zur Hausen capped this remarkable and significant achievement.

Pathology's contributions to the diagnosis of cervical, vaginal, and vulvar cancers and their precursors have also played an extremely important role, as the pathologic diagnosis provides the endpoint, and hence, proof of efficacy for the large clinical trials such as the ASC-US/LSIL Triage study (ALTS), which laid the foundation for the management of cervical precursors, and for the vaccine trials. Other developments that occurred during this time were the introduction of high-risk HPV DNA testing as a supplement to cytology for screening in concert with the development of The Bethesda System Classification (TBS), first for cervical cytology and subsequently for histopathology. The use of molecular biologic methods in conjunction with a histopathologic classification based on the natural history of the disease ushers in a new approach for surgical pathology, which undoubtedly will continue to evolve in the future.

Thus, the publication of this Fascicle marks the transition in diagnosis of lower genital tract lesions from a largely morphologic activity to one based upon integrated assessment using microscopy and molecular biology. Furthermore, the ability to integrate these diagnostic approaches with clinical data for patient management has been heightened. The introduction of vaccination in the community also thrusts pathology into a new unprecedented public health role with regard to disease monitoring, which will likely expand over time. Finally, the realization that cervical cancer is becoming increasingly preventable, carries with it both a sense of accomplishment and the recognition that this must now be translated into an achievable goal of cancer prevention in underdeveloped nations.

There are a number of significant changes in this edition of the Fascicle that are worthy of mention. Although the text has remained concise in order to maintain the primary function of the Fascicle as an atlas rather than a comprehensive textbook, it has been substantially updated to reflect the changes in the field as noted above. In this regard, the number of illustrations, all of which are in color, has almost doubled. Both the text and the photomicrographs emphasize the importance of immunohistochemistry and molecular in situ hybridization as adjuncts to morphology in routine clinical diagnosis. Although HPV infection was a separate chapter in the previous edition, it has been greatly expanded and updated in the present edition. A binary (low-grade and high-grade squamous intraepithelial lesion) classification for histology, analogous to TBS for cytology, replaces the four-tiered dysplasia/CIS system and the three-tiered CIN system. The binary classification has been controversial. This approach was advocated in the last edition and our experience since then has convinced us of its utility based on our (RJK, BMR, and MES) and our colleagues' (Mark Stoler, Alex Ferenczy, and Dorothy Rosenthal) collective experience reviewing over 100,000 cervical, vaginal, and vulvar biopsies as part of the pathology panels for the ALTS and Merck vaccine trials.

The publication of this Fascicle has depended on the assistance of many individuals to whom the authors are greatly indebted. We are especially grateful to Drs. Mark Stoler and Tom Bonfiglio for their thoughtful review and comments on the entire text. At Johns Hopkins, Ms. Evelyn Hinton, our Administrative Assistant, provided excellent secretarial assistance, and Mr. Norman Barker, Associate Professor and Director of Pathology, Digital Imaging and Computer Graphics reviewed and edited all of the photomicrographs, many of which required his considerable expertise since the images were scanned from Kodachrome slides. At the University of Florida, our program assistant, Ms Karen Hyde, provided valuable secretarial assistance. Drs. and Professors John Reith and Vladimir Vincek provided thoughtful review of the vulvar soft tissue and melanoma sections. Mr. Robin Foss, Associate Director of Surgical Pathology Services, provided expertise with the gross specimen photographs and digital imaging of the vulvar chapter. Finally, there are many individuals, including those from other disciplines who, through our collaboration with them, have enhanced our understanding of the pathobiology of neoplasms of the lower female reproductive organs. They are far too numerous to specifically mention, but their influence on us has been considerable. To all these people we wish to express our thanks.

Robert J. Kurman, MD

Brigitte M. Ronnett, MD

Mark E. Sherman, MD

Edward J. Wilkinson, MD

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1 EMBRYOLOGY OF THE LOWER FEMALE GENITAL TRACT

CERVIX AND VAGINA

The differential diagnosis of a number of benign and malignant lesions of the lower female genital tract is facilitated by an understanding of the embryology of these organs. In the past, our understanding of the embryology of the human cervix and vagina was based on experimental work in animals whose embryologic development differed from that of the human. These studies have been summarized by Forsberg (7), O'Rahilly (10), and Mossman (9). Subsequent studies in which human fetal genital tracts were implanted into athymic (nude) mice by Cunha and Robboy (4,11,13) have greatly advanced our understanding of the embryology of the human vagina. The discussion of the development of the cervix and vagina that follows is a brief account of what remains a complex and incompletely understood subject (12).

The anlage of the uterine corpus and cervix and the upper vagina is termed the uterovaginal canal. This structure develops from the fusion of the mesoderm-derived, paired müllerian ducts at about day 54 postconception. The canal is initially a straight tube lined by müllerian columnar epithelium, which joins the endoderm-derived urogenital sinus. The point at which the two meet is referred to as the müllerian tubercle (fig. 1-1). This site is destined to be the location of the vaginal orifice at the hymenal ring.

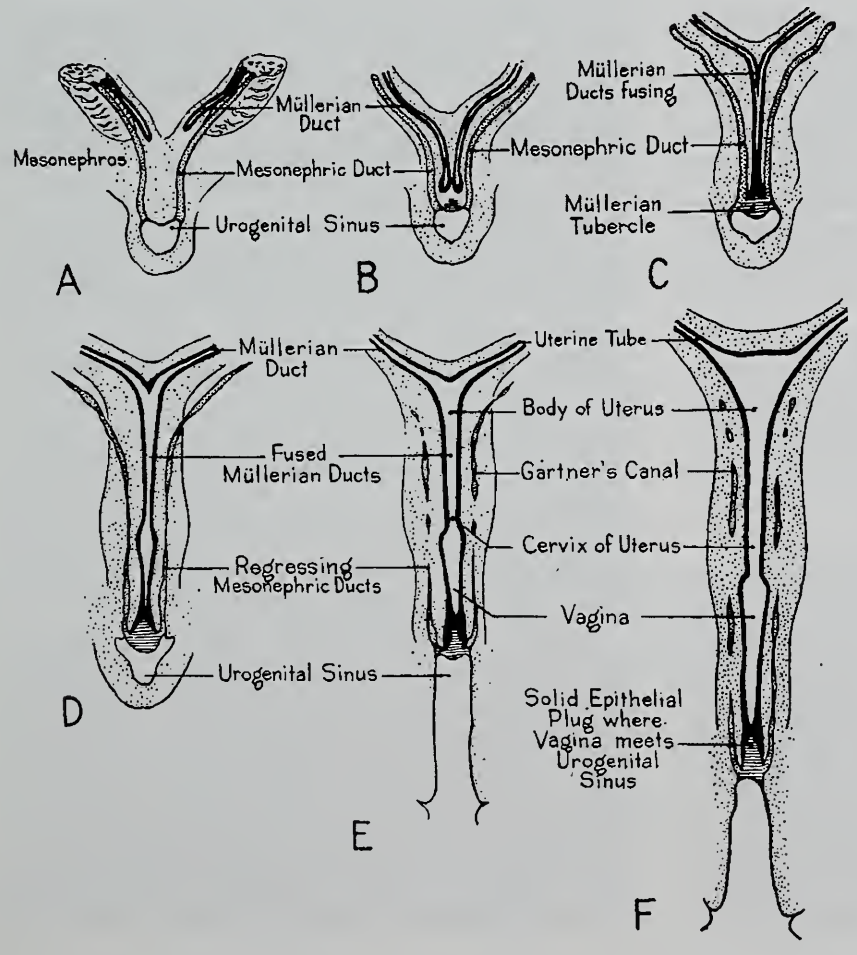

Figure 1-1

FUSION OF THE MÜLLERIAN DUCTS TO FORM THE UTERUS AND VAGINA

The close relationship of the epithelium of the müllerian ducts to the urogenital sinus explains, in part, the difficulty in determining which epithelium gives rise to that of the vagina. (Fig. 363 from Pattern BM. Human embryology. Philadelphia: Blakiston; 1953:580. Redrawn from Koff AK. Contrib Embryol 1933;24.)

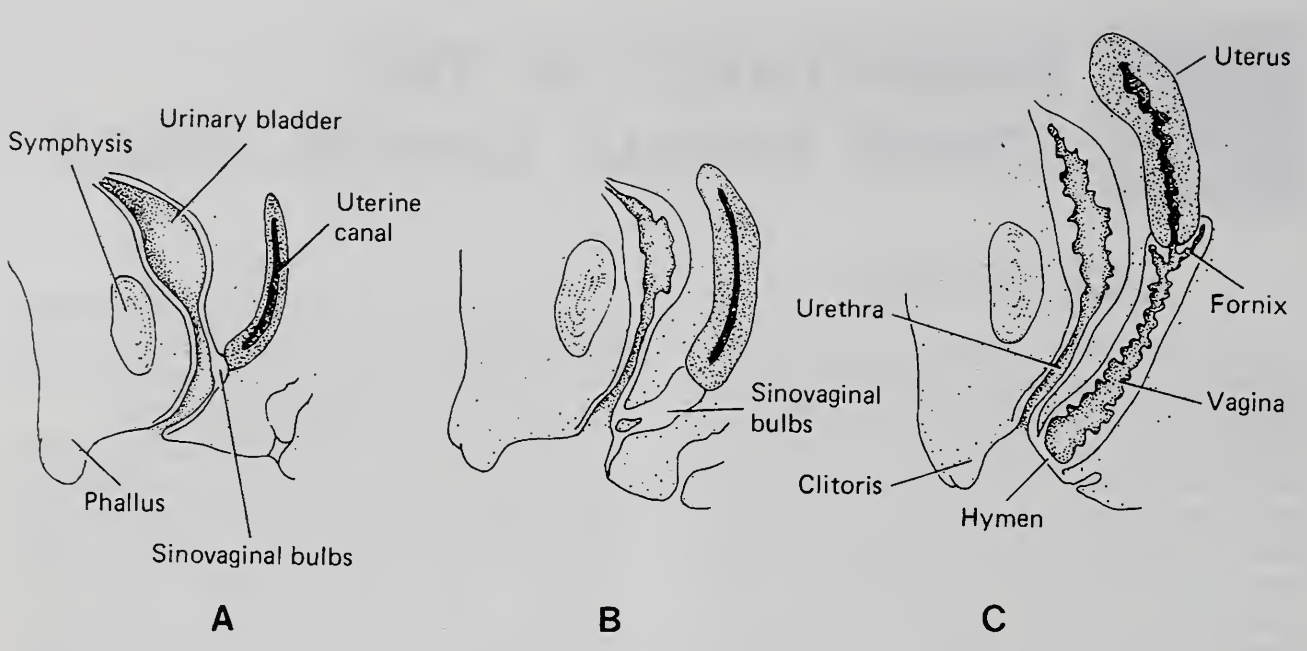

Figure 1-2

FORMATION OF THE UTERUS AND VAGINA

These sagittal sections show the formation of the uterus and vagina at various stages of development. (Fig. 15-24 from Sadler TW. Langman's medical embryology, 5th ed. Baltimore: William & Wilkins; 1985:267.)

At approximately day 66, the epithelium of the caudal uterovaginal canal begins to stratify, either as a result of cephalad migration of cells from the urogenital sinus (1,11) or by direct squamous transformation of the columnar cells lining the uterovaginal canal (6). Clinical evidence favoring the former interpretation is provided by women born with an imperforate, transverse vaginal septum (14). In these patients, the vagina lying above the septum is lined by columnar epithelium, whereas the vagina below the septum is lined by squamous epithelium. The stratification of cells in the region of the müllerian tubercle is the first evidence of the formation of the vaginal plate, a structure unique to humans. The stratified squamous epithelial cells of the vaginal plate proliferate, so that by day 77 the vagina is a nearly solid core of squamous epithelium (fig. 1-1). Endocervical glands and the vaginal fornices appear between 91 days (13th week) and the 15th week, thereby permitting the first definitive identification of the cervix (fig. 1-2). At this time, the vagina and cervix are highly sensitive to steroid hormones, and from about the 16th week of fetal life to birth the cervix responds to estrogenic stimulation by marked growth. Similarly, mucin secretion in endocervical glands begins in response to estrogenic stimulation during the 7th month of gestation and decreases rapidly during the first 2 postnatal weeks, remaining at a low steady state until menarche, when increased secretion begins again.

Experimental studies in rodents provide cogent evidence that the primitive epithelium lining the uterovaginal canal is programmed to differentiate into squamous, mucinous, and tuboendometrial-like epithelia by the underlying stroma. Murine neonatal vaginal epithelium grown on uterine stroma differentiates into columnar epithelium whereas uterine epithelium grown on vaginal stroma differentiates into squamous epithelium (2). The cytosolic proteins in the resultant epithelia reflect that of the induced rather than the original source (3).

Studies of the developing human genital tract implanted into nude mice have shown that the cervix and uterine corpus are invested by two layers of primitive mesenchyme (2,3). The inner layer is destined to become the endocervical and endometrial stroma and the outer layer the myometrium. The inner layer invests the uterine corpus and cervix, gradually tapering and ending at the point where the cervix joins the

vagina, and possibly extending into the vagina and vulva (5). The outer layer is continuous throughout the fallopian tube, myometrium, and wall of the vagina. It has been postulated that the inner layer induces differentiation of the tuboendometrial type glandular epithelium of the fallopian tube, uterine corpus, and deep glands in the cervix (4). According to this view, the squamous epithelium of the vagina that may be derived from the urogenital sinus is not subject to the inductive stimulus of the cervicovaginal mesenchyme.

The above concept of cervical and vaginal development is attractive because it offers an explanation for many of the genital tract abnormalities observed in women exposed to diethylstilbestrol (DES) and related drugs in utero. In the DES-exposed female fetus, the primary teratogenic effect of the drug may be directly on the stroma, which in turn induces abnormalities in the overlying epithelium. Indeed, in the nude mouse model it has been shown that in utero DES inhibits the usual segregation of the inner and outer layers of the mesenchyme that surround the cervicovaginal canal (13). A similar mechanism may be involved in the gross structural abnormalities of the cervix (hoods, ridges, cervical hypoplasia, and vaginal fornix hypoplasia) and the abnormal contours of the endometrial cavity (uterine constriction and T-shaped uterus) that have been observed in human females exposed to DES in utero (8). In addition, enlargement of the transformation zone, evident in most DES-exposed women, may be due to a failure in the normal segregation of the underlying mesenchyme into discrete layers. As a result, the innermost layer of mesenchyme extends out laterally and cephalad beneath the ectocervix and upper vagina. This mesenchyme induces the differentiation of mucinous epithelium, i.e., the glandular component of the transformation zone, which in turn extends over the ectocervix and upper vagina. In the latter location, this results in mucinous type adenosis. Failure of the upgrowth of urogenital sinus squamous epithelium results in retention of the original embryonic müllerian epithelium and contact with the mesenchyme of the vagina results in induction of tuboendometrial type glandular epithelium (adenosis) in the more caudal portion of the vagina (fig. 1-3)

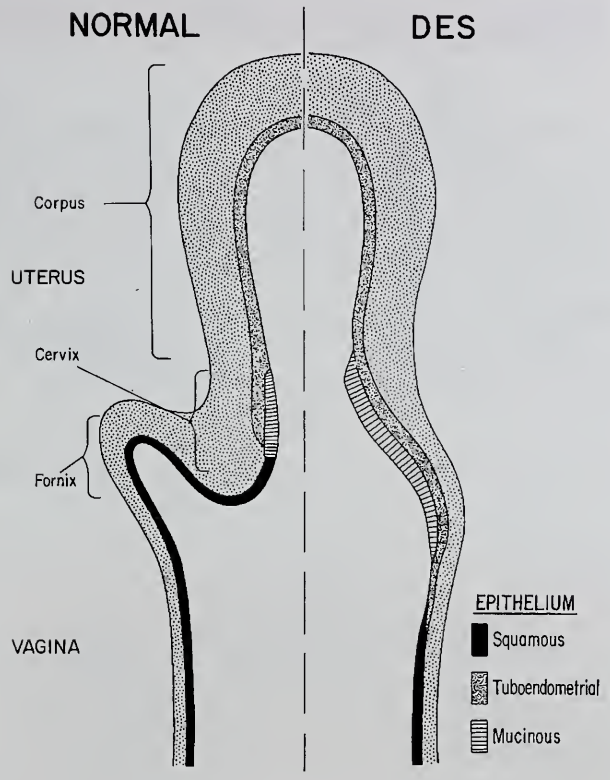

Figure 1-3

HYPOTHETICAL CONSEQUENCES OF PRENATAL DIETHYLSTILBESTROL EXPOSURE TO DEVELOPING VAGINA AND CERVIX

A normal genital tract is illustrated on the left. The genital tract in a patient exposed to diethylstilbestrol (DES) in utero is illustrated on the right. (Fig. 2 from Robboy SJ. A hypothetic mechanism of diethylstilbestrol (DES)-induced anomalies in exposed progeny. Hum Pathol 1983;14:832.)

(11). Clear cell carcinoma in the DES-exposed woman is characteristically associated with tuboendometrial type adenosis rather than with mucinous adenosis.

VULVA

The formation of the vulva becomes evident in the 4th embryonic week, when proliferation of the mesodermal stroma adjacent to the cloaca results in elevation of the overlying ectoderm. Ventrally, this results in the formation of the genital tubercle, which is destined to become the clitoris, while laterally, two parallel ridges, each composed of a medial and lateral fold, develop. The medial folds, or urogenital folds, develop into the labia minora. The lateral folds, or labioscrotal folds, develop into the labia majora.

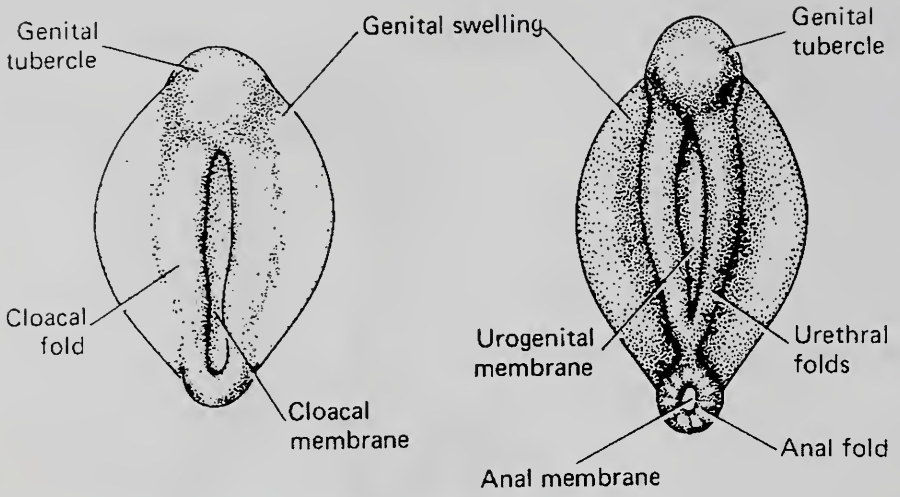

Figure 1-4

EMBRYOLOGY OF THE VULVA

The indifferent stage of the external genitalia is represented at approximately 4 weeks (left) and at approximately 6 weeks (right). (Fig. 15-26 from Sadler TW. Langman's medical embryology, 5th ed. Baltimore: William & Wilkins; 1985: 269.)

Table 1-1

FEMALE AND MALE HOMOLOGUES OF THE EXTERNAL GENITALIA OF THE HUMAN

Female	Male
Vulvar vestibule	Distal urethra
Skene glands	Prostate gland
Bartholin glands	Cowper glands (bulbourethral glands)
Minor vestibular glands	Glands of Littre
Clitoris	Corpus cavernosum of the penis
Labia minora	Corpus spongiosus of the penis
Labia majora	Scrotum

By the end of the 6th week of development the urorectal septum and the cloacal plate fuse to form the urogenital membrane anteriorly and the anal membrane posteriorly. Fusion of the lower portion of the labioscrotal folds anterior to the anal fold results in the formation of the perineum (fig. 1-4). Thus, the epithelia of the labia majora, the labia minora, and the clitoris are of ectodermal origin.

The bilateral labioscrotal folds fuse anterior to the genital tubercle to form the mons pubis. The junction of the distal vagina with the urogenital sinus results in the development of the vulvar vestibule, which is identifiable by the 16th week. Except for a small area immediately anterior to the urethra, which may be of ectodermal origin, the vestibule is of endodermal origin. The junction of the epithelium derived from endoderm and that derived from ectoderm is seen in the adult on the inner aspects of the labia majora and is marked by the presence of sebaceous glands underlying the epithelium derived from ectoderm evident on the medial aspects of the labia majora (see chapter 2). The Bartholin gland, the major gland of the vestibule, is of endodermal origin. Homologous structures of the male and female are compared in Table 1-1.

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2 ANATOMY OF THE LOWER FEMALE GENITAL TRACT

The following discussion focuses primarily on those aspects of the gross anatomy and lymphatic drainage that are pertinent to the evaluation of tumors in the lower female genital tract. For a comprehensive review of the gross anatomy of the cervix, vagina, and vulva, the reader is directed to accounts by Krantz (16) and Friedrich (8).

CERVIX

Gross Anatomy

The cervix accounts for half to a third of the length of the uterus. It measures 2.5 to 3.0 cm in length and 2.0 to 2.5 cm in diameter. The vaginal portion of the cervix (portio vaginalis, or ectocervix) is surrounded by a reflection of the vaginal wall termed the fornix. The portion of the cervix lying above the upper margin of the vagina abuts anteriorly on the bladder, and is separated from it by loose connective tissue that extends into the broad ligaments laterally. Posteriorly, the upper cervix is covered by peritoneum forming the lining of the cul-de-sac. The connective tissue surrounding the cervix and vagina extends laterally and posteriorly toward the second to fourth dorsal vertebrae as the uterosacral ligaments. The chief support of the cervix, however, is from the cardinal ligaments, which are fibromuscular bands that fan out laterally from the lower uterine segment, including the cervix, to the lateral pelvic walls (fig. 2-1).

Lymphatic Drainage

The cervix has a complex lymphatic drainage system that is arranged in three beds. One bed underlies the epithelium of the endocervical clefts and squamous epithelium; a second bed lies deeper in the stroma. Both beds drain into perforating lymphatic vessels, which in turn empty into a serosal plexus; the latter drains a third bed from the outer surface of the cervix. The lymphatic channels leave the cervix via two main vessels closely related to the uterine artery, which fan out anteriorly and laterally in the broad ligament, and a third vessel, which

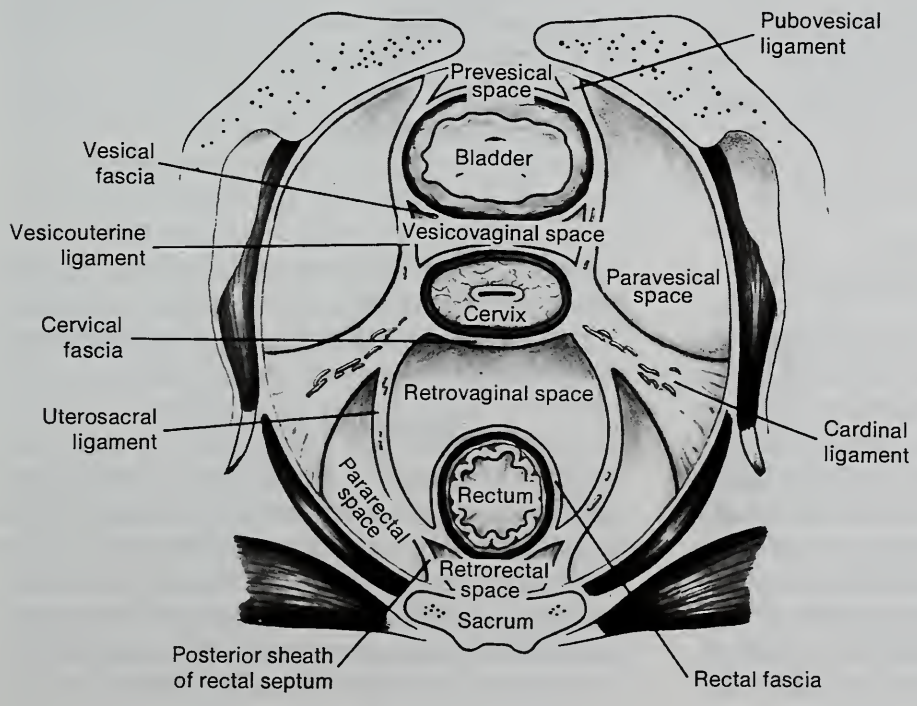


Figure 2-1

CROSS SECTION OF THE PELVIS AT THE LEVEL OF THE CERVIX

This schematic illustrates a cross section of the pelvis at the level of the cervix. (Fig. 3-10 from DiSaia PJ, Creasman WT. Clinical gynecologic oncology, 3rd ed. St. Louis: CV Mosby; 1989:85.)

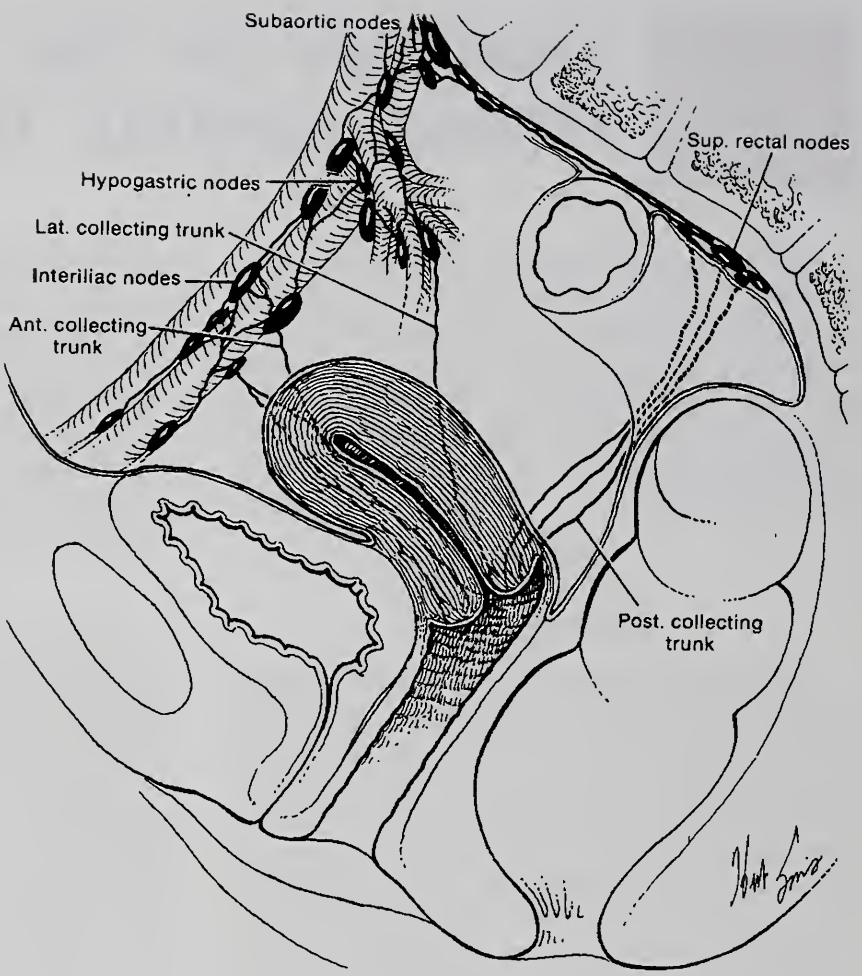


Figure 2-2

LYMPHATIC DRAINAGE OF THE CERVIX

The main lymphatic trunks and lymph nodes of the uterine cervix are illustrated. (Fig. 14-8 from Schmidt WA. Principles and techniques of surgical pathology. Menlo Park, CA: Addison-Wesley; 1983:439.)

progresses posterolaterally in the uterosacral ligaments toward the sacrum. The pelvic lymph nodes into which these lymphatics drain are divided into three main groups (fig. 2-2): the external iliac nodes lie along the external iliac vessels, the internal iliac nodes along the internal iliac arteries, and the common iliac nodes along the common iliac arteries (10).

Colposcopic Features and Microscopic Anatomy

The bulk of the cervix is composed of fibromuscular tissue, of which fibrous tissue is the predominant component. The epithelium that lines the cervix is of three types: native squamous epithelium, glandular epithelium, and metaplastic squamous epithelium. Early studies by Kaufmann and Ober (15) revealed that squamous intraepithelial lesions (cervical intraepithelial neoplasia, dysplasia-carcinoma in situ) are almost always immediately above the glandular epithelium, suggesting that neoplasia arises in squamous epithelium that is derived from glandular epithelium. The area of the cervix where the glandular epithelium undergoes metaplastic transformation to squamous epithelium is referred to as the transformation zone, or T-zone. The squamocolumnar junction (SCJ) is the most apical (superior) margin of the transformation zone. At the SCJ, metaplastic squamous epithelium joins columnar epithelium. An awareness of the colposcopic and microscopic features of both the metaplastic squamous epithelium and the transformation zone is important to appreciate the pathology of cervical neoplasia.

Squamous Epithelium

On colposcopic examination, the native squamous epithelium is smooth and pink; blood vessels are not clearly discernible. The epithelium proliferates, matures, and exfoliates under the influence of estrogenic stimulation; in contrast, progesterone inhibits maturation of squamous epithelium. The epithelium is

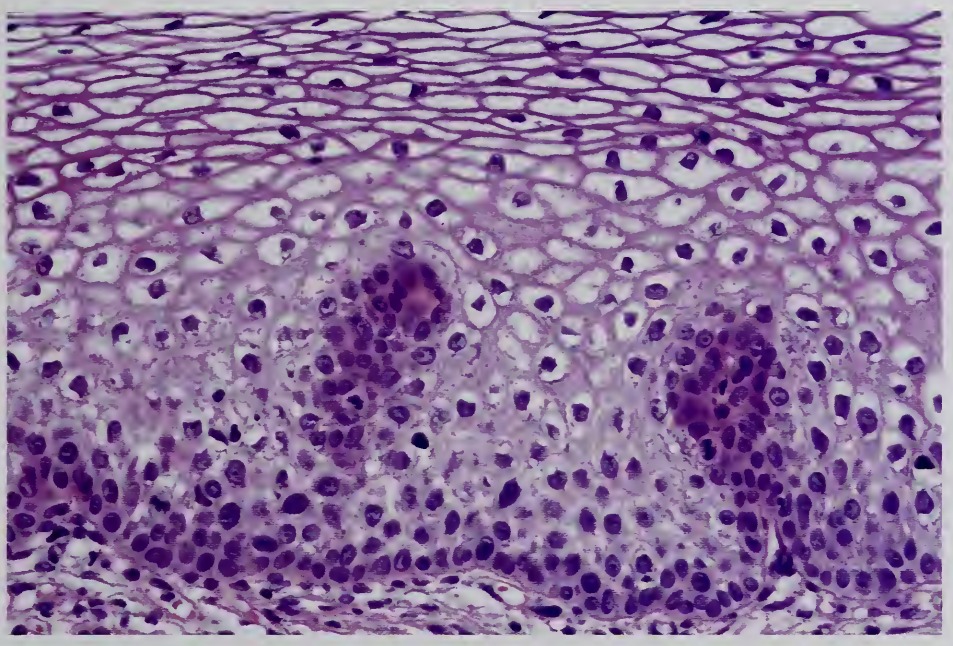


Figure 2-3

NORMAL (NATIVE) SQUAMOUS EPITHELIUM OF CERVIX

Mature glycogenated squamous epithelium is composed of three zones (parabasal, intermediate, and superficial). As cells approach the surface, their nuclei become progressively smaller and their cytoplasm becomes more abundant.

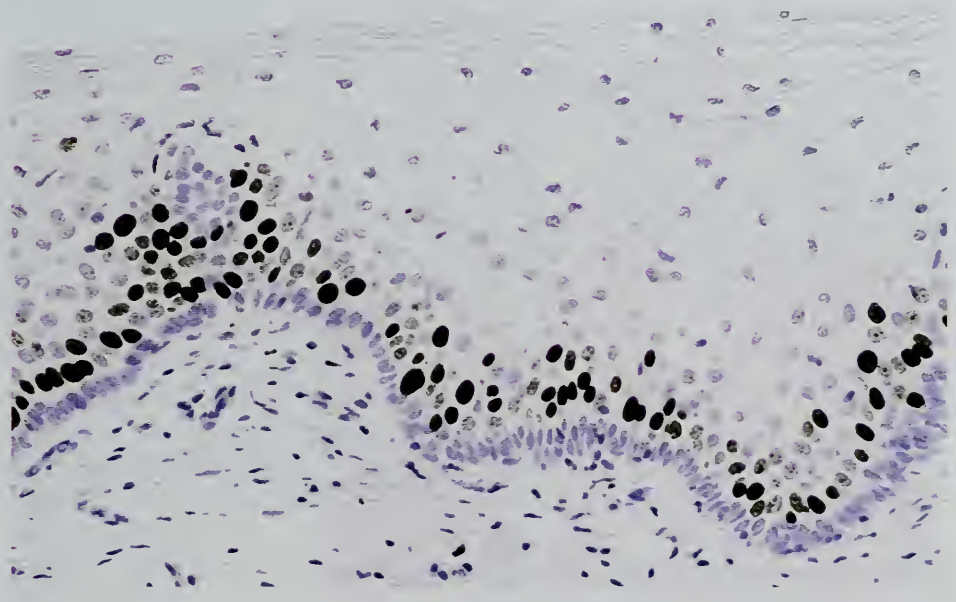


Figure 2-4

NORMAL SQUAMOUS EPITHELIUM OF CERVIX

Proliferating cells, as indicated by nuclear expression of Ki-67, are confined to the parabasal zone; reserve cells do not exhibit proliferative activity.

composed of squamous cells with a spectrum of maturation, and is divided into three zones based on the degree of maturation (fig. 2-3). The lower third constitutes the basal/parabasal zone, which is composed of basal reserve cells situated perpendicular to the basement membrane and parabasal cells having uniform oval nuclei and limited eosinophilic cytoplasm. In normal squamous epithelium, proliferation is limited to the basal/parabasal zone. In regions where the reserve cell layer is prominent and distinct from the parabasal cells, immunoreactivity for Ki-67, a proliferation marker, is confined to the nuclei of parabasal cells (but not reserve cells) (fig. 2-4). In normal maturing squamous epithelium with mild proliferative activity in the parabasal zone, the reserve cell layer may be less conspicuous and Ki-67 proliferative activity may be evident in some basal as well as parabasal cells (fig. 2-5).

The middle third of the epithelial zone is designated the intermediate zone and consists of cells with smaller, round to oval, uniform nuclei and increased amounts of cytoplasm, resulting in cells having lower nuclear-cytoplasmic ratios compared with parabasal cells. Maturation occurs in the intermediate zone and is manifested

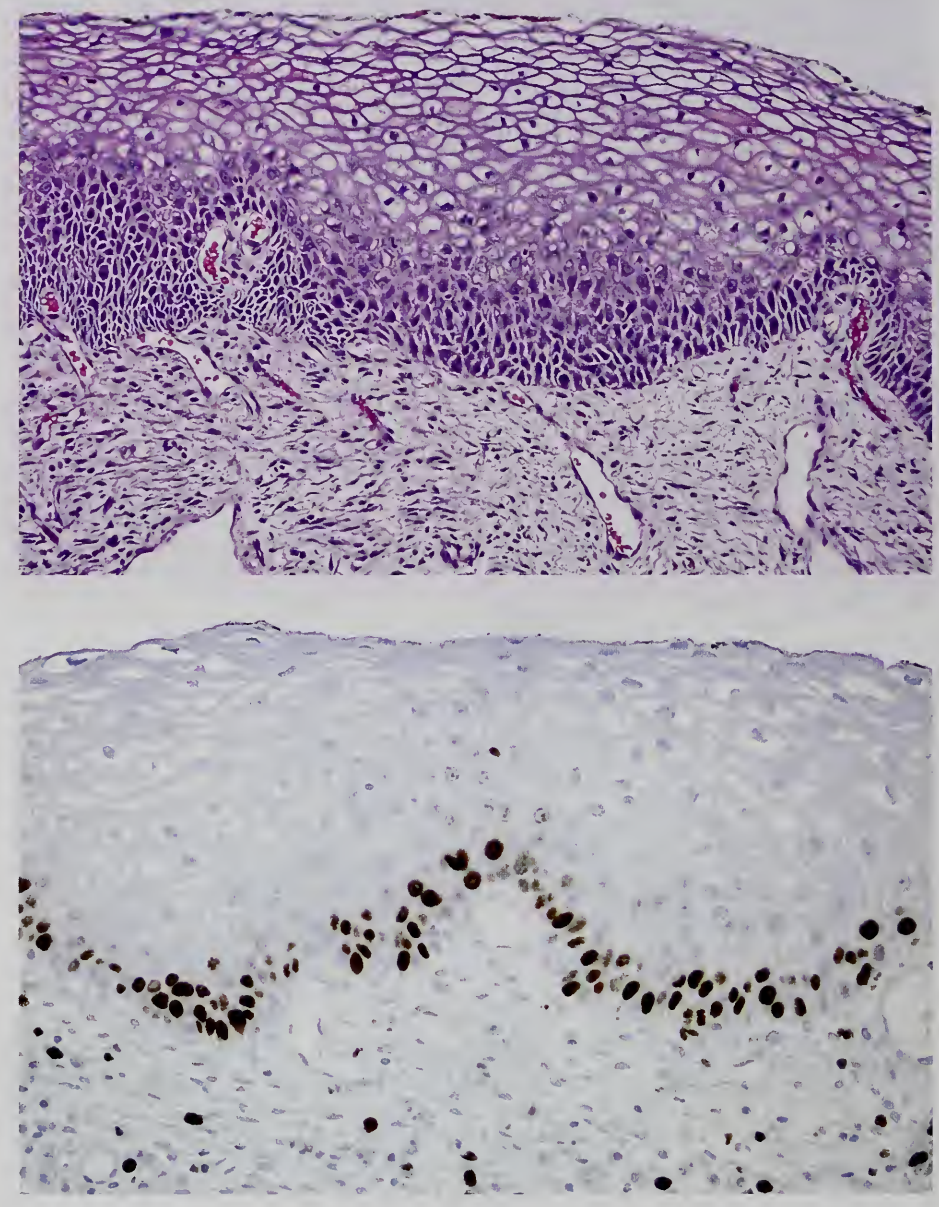


Figure 2-5

MATURE SQUAMOUS MUCOSA OF CERVICAL TRANSFORMATION ZONE

Top: Glycogenated squamous epithelium from the transformation zone displays a slightly more prominent parabasal layer and inconspicuous reserve cell layer compared with the example in figure 2-3. Squamous epithelium of the transformation zone is indistinguishable from native squamous epithelium, and is identified as metaplastic in origin when endocervical glands are found beneath the squamous epithelium (see figures 2-9 and 2-13).

Bottom: Similar to native squamous epithelium, proliferating cells, as indicated by nuclear expression of Ki-67, are confined to the parabasal zone in mature squamous epithelium that is metaplastic in origin; reserve cells are inconspicuous.

by an increase in the amount of cytoplasm and the accumulation of abundant glycogen. This is responsible for the clear, vacuolated appearance of the cells in routine sections and for their uptake of iodine with the Schiller test.

The upper third is the superficial zone, which contains terminally differentiated mature squamous cells having abundant cytoplasm and small, round to elongated pyknotic nuclei. The degree of maturation varies according to the hormonal status of the individual. In the premenarchal girl and postmenopausal woman, the squamous epithelium undergoes little, if any, maturation and is composed almost entirely of basal and parabasal cells.

Endocervical Glandular Epithelium

The endocervical epithelium, as shown by three-dimensional studies, is not truly glandular but consists of deep cleft-like foldings of the surface epithelium into the underlying stroma to a usual depth of approximately 5 mm (7), resulting in papillary surface mucosal architecture (fig. 2-6). In cross section, the complex infoldings appear to be isolated glands. Colposcopic examination, after the application of 3 to 5 percent acetic acid, reveals that the glandular epithelium covers villous-like structures, each of which contains a central capillary. The villi are clustered together, resembling a bunch of

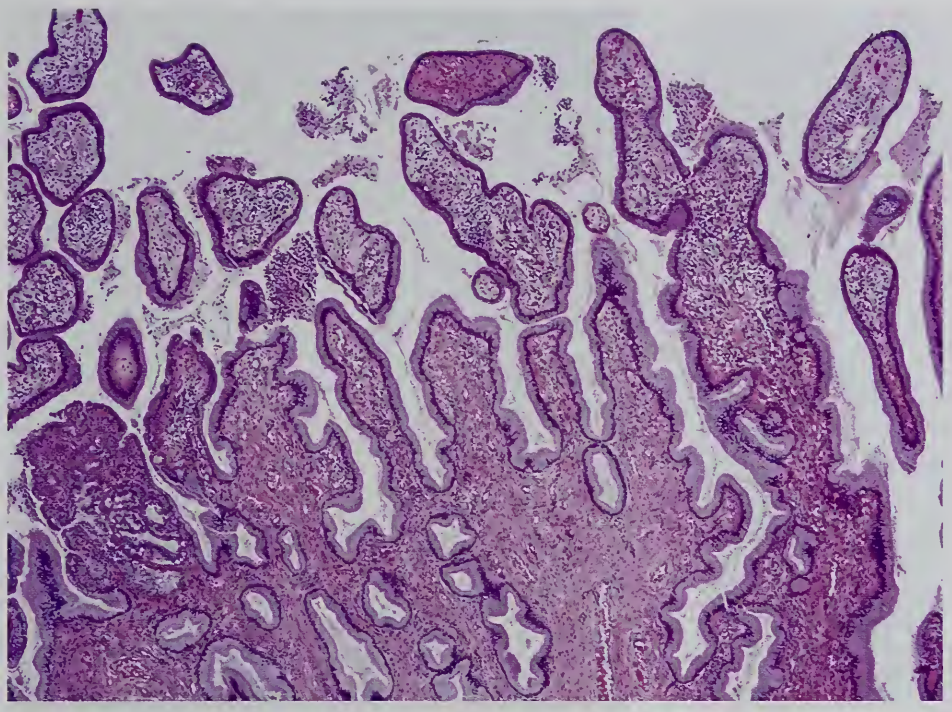


Figure 2-6

NORMAL ENDOCERVICAL MUCOSA

Left: The mucosa has a papillary configuration created by invaginations and cleft-like foldings of endocervical glandular epithelium into the stroma. Tangentially sectioned clefts deeper in the stroma have the appearance of discrete glands.

Below: Papillary projections and clefts are lined by columnar mucinous epithelium.

grapes. In 70 percent of sexually active women in the reproductive age group, the glandular epithelium extends onto the ectocervix (19). To the naked eye, the glandular epithelium appears red because of the rich subepithelial capillary network and, consequently, has been referred to as cervical erosion or ectropion. Since this appearance of the cervix is normal in most women and is a manifestation of the normal transformation zone, the term "erosion" is erroneous; the designation *ectropion* is most widely used for this phenomenon.

Microscopically, the villous structures are rounded, vascular stromal papillae lined by endocervical epithelium. The stroma of the papillae typically contains small numbers of chronic inflammatory cells, the presence of which does not warrant a diagnosis of chronic cervicitis. In contrast, large numbers of lymphocytes, plasma cells, or aggregates of lymphocytes with follicular centers justify a diagnosis of chronic cervicitis. The glandular epithelium of the cervix is composed of a single layer of columnar cells with basal round to oval nuclei and finely granular cytoplasm containing abundant mucin (fig. 2-7). Some of the cells may be ciliated. Argyrophilic cells are detected in ectocervical epithelium in up to 50 percent of specimens examined. Some of the argyrophilic cells contain immunoreactive serotonin; those cells that are serotonin negative are positive for chromogranin and epithelial membrane antigen (6). Mitotic activity is not observed in endocervical epithelial cells under

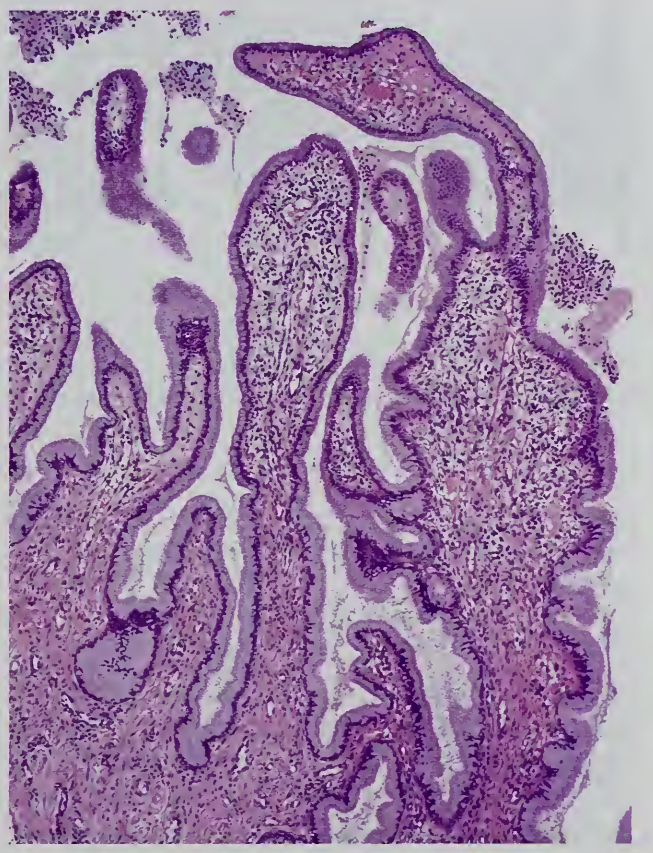


Figure 2-7

NORMAL ENDOCERVIX

Endocervical glandular epithelium is composed of columnar cells with abundant mucinous cytoplasm and small, basally situated nuclei with uniform chromatin.

Figure 2-8

COLPOPHOTOGRAPH OF CERVICAL TRANSFORMATION ZONE WITH SQUAMOCOLUMNAR JUNCTION

The squamocolumnar junction is visualized where the smooth, flat, white squamous epithelium of the upper lip of the cervix joins the glistening, papillary, tan mucosa of the endocervix.

normal circumstances, consistent with the view that these cells are derived from subcolumnar reserve cells (26).

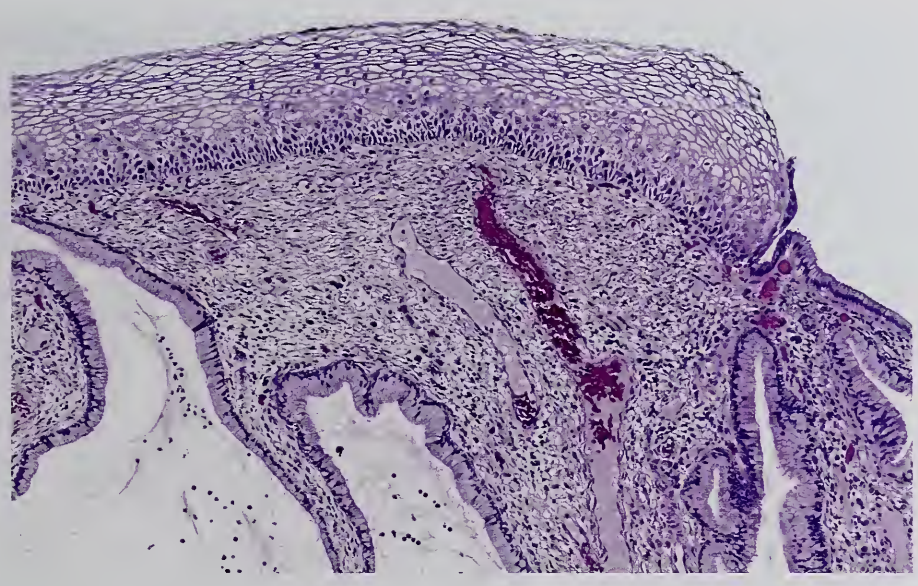
Transformation Zone

The transformation zone is bounded distally by the original squamocolumnar junction and proximally by the new squamocolumnar junction (junction of metaplastic squamous epithelium and unaltered endocervical glandular epithelium) (figs. 2-8, 2-9). Although it was previously believed that the original squamocolumnar junction was at the external os, studies by Pixley (19) have shown that it is on the ectocervix in 70 percent of fetuses. The original squamocolumnar junction can be identified with the colposcope by the finding of residual gland openings surrounded by metaplastic squamous epithelium at the outer limit of the transformation zone. This site corresponds histologically to the most distal gland that is covered by squamous epithelium. The distal boundary of the transformation zone remains constant throughout life. In contrast, the boundary between the metaplastic squamous epithelium and the endocervical glandular epithelium shifts. With the onset of puberty or in pregnancy, the cervix increases in volume and the glandular epithelium is everted onto the ectocervix. After the menopause, with a reduction in the size of the cervix, the glandular epithelium retracts into the endocervical canal

Figure 2-9

CERVICAL TRANSFORMATION ZONE WITH SQUAMOCOLUMNAR JUNCTION

Mature squamous epithelium is identified as being from the transformation zone, and hence, metaplastic in origin, by its location over endocervical glandular epithelium. The actual squamocolumnar junction is situated where squamous epithelium abuts endocervical glandular epithelium along the surface (right).



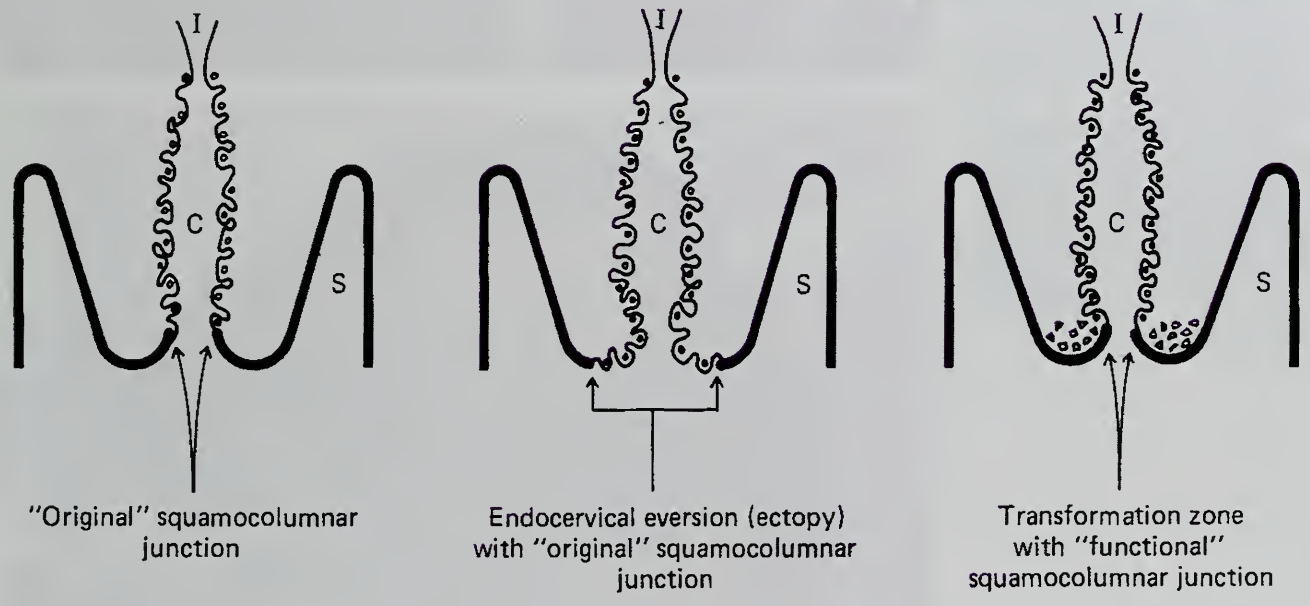


Figure 2-10

THREE TYPES OF SQUAMOCOLUMNAR JUNCTIONS

The portio is completely covered by native squamous epithelium, with the squamocolumnar junction at the external os (left). An ectropion has the squamocolumnar junction on the exocervix below the external os (middle). An ectropion covered by squamous epithelium forms the cervical transformation zone; the new or functional squamocolumnar junction of the transformation zone is at the external os (right). C = endocervical columnar epithelium; I = uterine isthmus; S = squamous epithelium. (Fig. 5.15 from Wright TC, Ferenczy A. Anatomy and histology of the cervix. In: Kurman RJ, ed. Blaustein's pathology of the female genital tract, 5th ed. New York: Springer-Verlag; 1987:148.)

(fig. 2-10). Once metaplastic squamous epithelium develops, it is permanent and does not normally revert to glandular epithelium. Thus, over time, the amount of squamous epithelium increases. As it matures, metaplastic squamous epithelium becomes indistinguishable from the native squamous epithelium. Squamous metaplasia is most active during late fetal life, adolescence, and pregnancy.

The first stage of metaplasia that is recognizable with the colposcope is characterized by the development of a slightly opaque glaze over the grape-like villous structures, corresponding to replacement of the glandular epithelium by

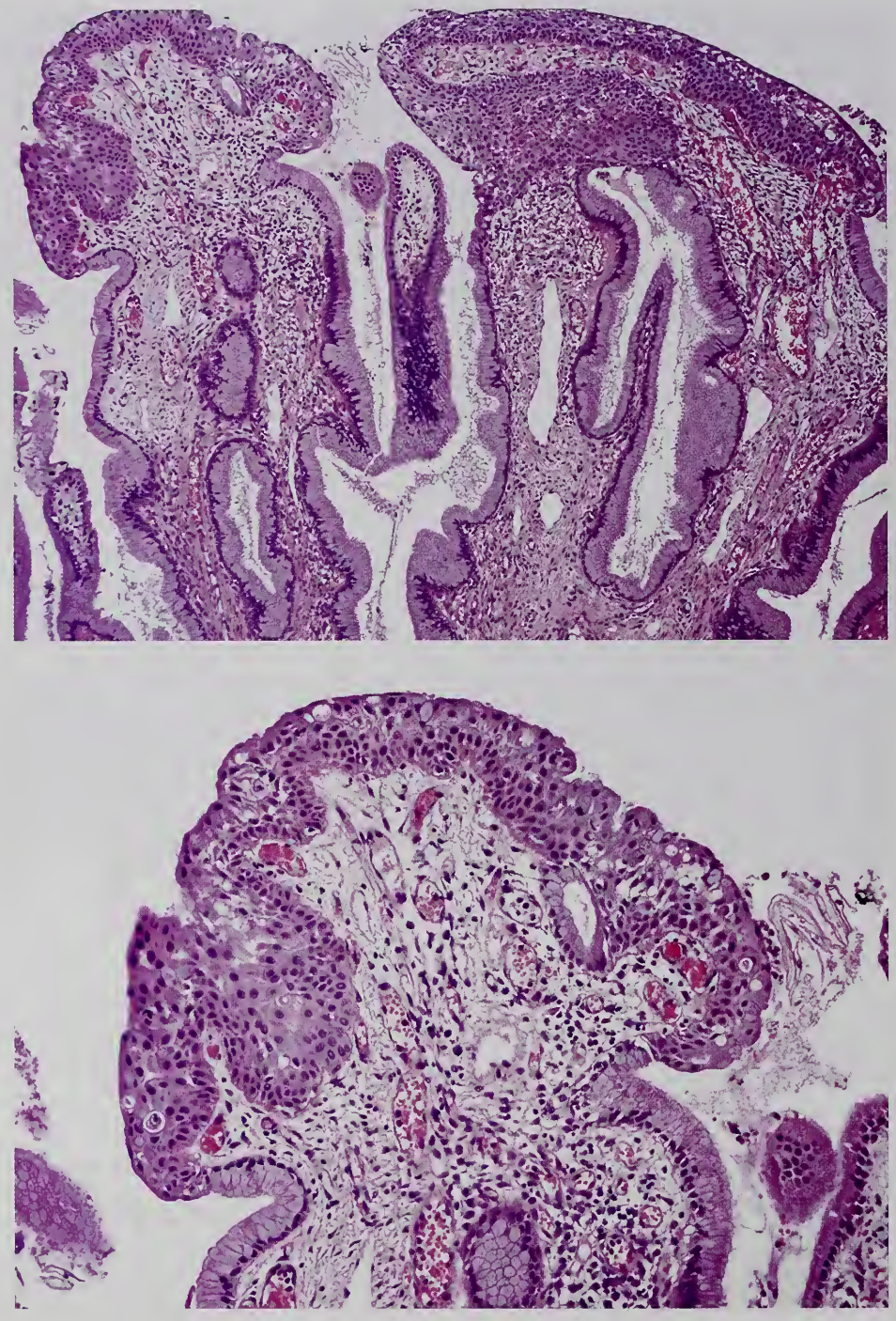


Figure 2-11

CERVICAL TRANSFORMATION ZONE

Top: Early squamous metaplasia is evident at the tips of the endocervical papillae where immature squamous metaplastic epithelium replaces the columnar mucinous epithelium.

Bottom: Immature squamous metaplastic epithelium covers the tip of an endocervical papilla where it has replaced the native mucinous epithelium. Rare mucinous cells are retained within the zone of metaplastic epithelium.

immature squamous metaplastic epithelium (fig. 2-11). The tips of the villous structures fuse and then disappear as they become replaced by patches of smooth, slightly pink, metaplastic epithelium (fig. 2-12). After the application of 3 to 5 percent acetic acid, the metaplastic epithelium appears faintly white. The immature metaplastic epithelium undergoes maturation but can be identified as metaplastic in origin, and hence, within the transformation zone, by the presence of endocervical glands beneath the mature squamous epithelium (fig. 2-13).

The initial stimulus for metaplasia is generally believed to be the lower (acid) pH of the vagina, which inactivates the buffering effect of the mucin that protects the columnar epithelium. Estrogen and progesterone may also play a role in this process.

The origin of metaplastic squamous cells has been the subject of controversy for over 50 years.

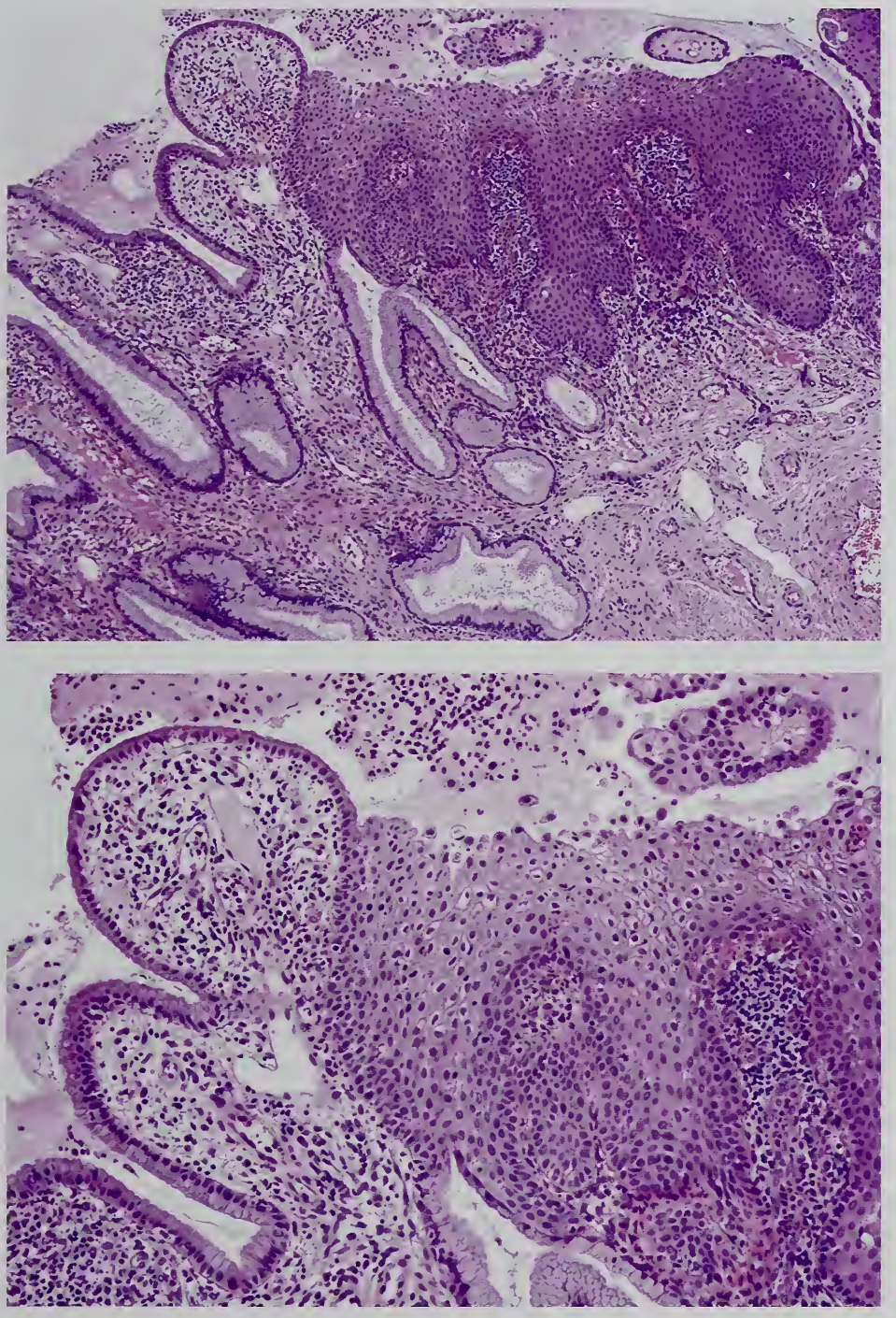


Figure 2-12

CERVICAL TRANSFORMATION ZONE

Top: As the process of squamous metaplasia progresses, the metaplastic epithelium matures and extends along the surface and into endocervical glandular clefts, resulting in fusion of adjacent endocervical papillae.

Bottom: Maturing squamous metaplastic epithelium acquires recognizable parabasal and intermediate zones.

Recent immunohistochemical and two-dimensional gel electrophoresis studies have provided compelling evidence that these cells are derived from subcolumnar reserve cells (9,26). Using antibodies against a restricted group of cytokeratins that are consistently expressed in reserve cells, Weikel et al. (26) identified reserve cells in all 26 uteri that they studied. The reserve cells contained cytokeratins that are general markers of squamous epithelium but did not contain cytokeratins found in keratinizing squamous epithelium. In addition, subcolumnar reserve cells exhibited cytokeratins typically found in simple glandular epithelia, including endocervical epithelium. Vimentin was not identified in subcolumnar reserve cells, precluding their derivation from stromal cells, as had been previously suggested. Thus, subcolumnar reserve cells appear to be facultative progenitor cells with the capacity to differentiate into either columnar or metaplastic squamous epithelium.

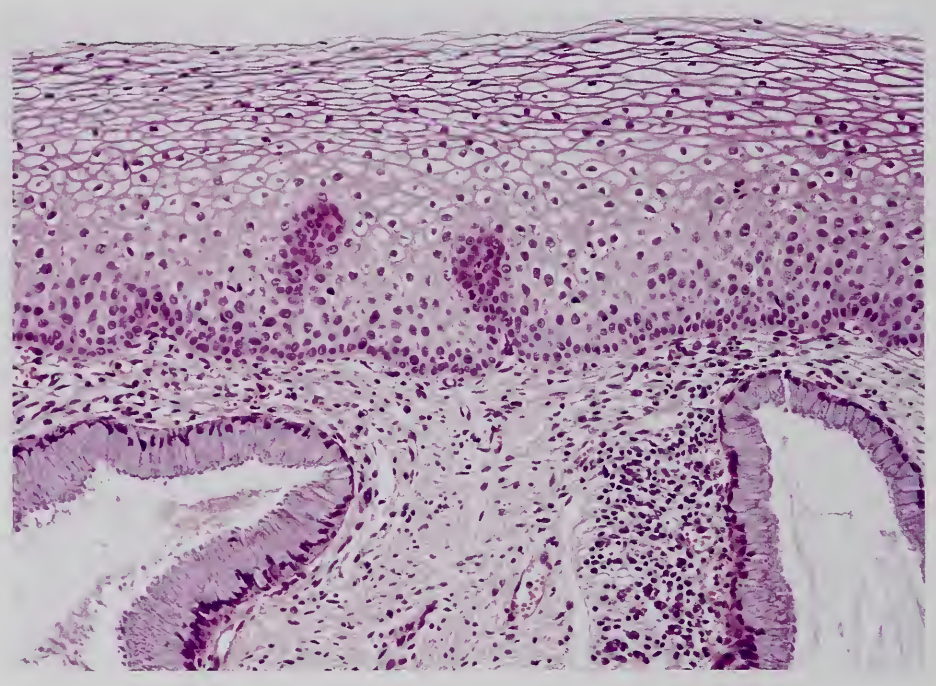


Figure 2-13

CERVICAL TRANSFORMATION ZONE

Mature squamous epithelium is identified as being from the transformation zone, and hence, metaplastic in origin, by its location over endocervical glandular epithelium.

VAGINA

Gross Anatomy

The vagina varies from 7 to 10 cm in length, opening into the vestibule and terminating in a circular fold around the cervix to form the vaginal fornices. The vagina lies ventral to the rectum and dorsal to the bladder, forming a 90° angle with the normal anteverted uterus so that the long axis of the endocervical canal is at a right angle to the long axis of the vagina. The cervix is directly opposite the posterior wall of the upper vagina.

Lymphatic Drainage

The lymphatics of the vagina are closely related to those of the cervix and vulva. The superior groups of lymphatics follow the cervical vessels along the uterine artery, terminating in the external iliac lymph nodes. The middle groups, which drain most of the vagina, terminate in the hypogastric nodes. The inferior groups drain the area around the hymen and anastomose partly with the middle groups and partly with those of the vulva, terminating in the inguinal lymph nodes.

Microscopic Anatomy

The squamous epithelium of the vagina closely resembles that of the native squamous epithelium of the cervix; normally, keratinization does not occur. Unlike the cervix, the vagina contains no glands. Proliferation, maturation, and desquamation of the squamous epithelium are similar to those in the cervix and are influenced by estrogens and progesterone. Thus, the thickness of the vaginal epithelium varies at different times during life.

Studies analyzing keratin expression have shed light on the process of vaginal proliferation and differentiation (23) by demonstrating that as cells ascend from the parabasal layer (proliferation compartment), they pass through a bipotential state prior to becoming committed to either keratinizing or nonkeratinizing differentiation. Keratins are reliable markers for characterizing cells that cannot be classified on the basis of morphologic criteria. Based on electrophoresis and immunoblotting studies, keratinizing differentiation is characterized by cytokeratin (CK)10 expression and nonkeratinizing differentiation by CK13 expression. These studies, in conjunction with immunostaining for proliferation markers (Ki-67 [MIB-1]), have led investigators to propose the following model of vaginal differentiation. Cells in the parabasal cell layer that express Ki-67 do not express CK10 or CK13. In the intermediate cell layers, squamous cells have the potential to differentiate in either keratinizing or nonkeratinizing directions as cells in this location express both CK10 and

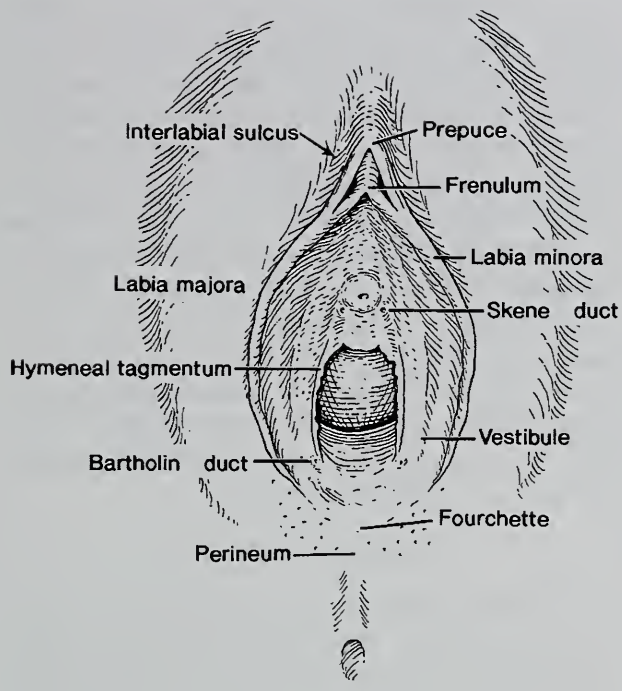


Figure 2-14

TOPOGRAPHY OF THE VULVA

The female external genitalia are identified in this schematic. (Fig. 1 from Wilkinson EJ, Hardt NS. Vulva. In: Sternberg SS, ed. Histology for pathologists. New York: Raven Press; 1992:866.)

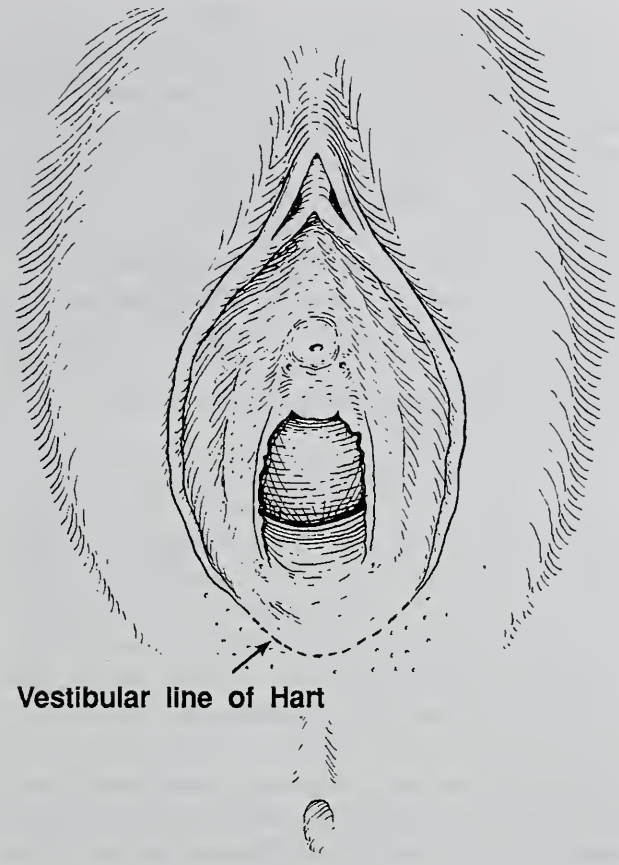


Figure 2-15

VESTIBULAR LINE OF HART

The dotted line in this schematic defines the junction between the sebaceous gland-bearing area of the perineal body and the inferior labia majora. The lateral dark lines define the vestibular line of Hart as it extends up to the prepuce. Individual variations may occur. (Fig. 2 from Wilkinson EJ, Hardt NS. Vulva. In: Sternberg SS, ed. Histology for pathologists. New York: Raven Press; 1992:866.)

CK13. As the squamous cells move into the superficial layers, they become terminally differentiated and are committed to either keratinizing or nonkeratinizing differentiation manifested by expression of either CK10 or CK13.

A 0.5 to 5.0 mm subepithelial stromal zone extends from the endocervix to the vulva (4). This zone is composed of stromal cells with myofibroblastic features (uniform with small, spindle-shaped nuclei); occasionally, however, cells have bizarre nuclei, similar to those present in vaginal mesodermal stromal polyps. It has been suggested that polyps and sarcoma botryoides may originate in this inconspicuous stromal zone.

VULVA

Gross Anatomy

The vulva is delimited by the mons pubis anteriorly, the anus posteriorly, and the inguinal-gluteal folds laterally (fig. 2-14). The hymenal ring marks the medial-superior aspect of the vulva. The major structures of the vulva include the labia majora and minora, the clitoris with its prepuce and frenulum, the vulvar vestibule, and the urethral meatus. The hymen is the most distal structure of the vagina and the most proximal boundary of the vulvar vestibule. It may be imperforate, round, annular, septate, cribriform, or porous. The hymen has nonkeratinized stratified squamous epithelium, which becomes glycogenated following estrogen exposure, as seen in women of reproductive age, newborn female infants, and postmenopausal women receiving oral or vaginal estrogen therapy.

The vulvar vestibule corresponds to the male distal urethra. It is the portion of the vulva that extends externally from the most medial external edge of the hymen to the vestibular line of

Hart (fig. 2-15). The latter is defined as the junction of the nonkeratinized squamous mucosa of the vestibule with the surrounding keratinized skin (11). The vaginal introitus is within the vestibule as are the orifices of the major vestibular or Bartholin glands, the periurethral orifices of Skene glands, and the orifices of the minor vestibular glands. The vestibular mucosa has the same gross and microscopic appearance as the vaginal epithelium and becomes glycogenated with exposure to estrogen. It has an epithelial thickness of approximately 1 mm when glycogenated (24).

The Bartholin glands are bilateral tubuloalveolar glands located beneath the hymen, labia minora, and labia majora in the posterior lateral area of the vulva. The Bartholin glands correspond to the male bulbourethral glands, or Cowper glands. The Bartholin duct, which measures approximately 2.5 cm in length, enters the vestibule posterolaterally, adjacent and immediately exterior (distal) to the hymen.

The periurethral, or Skene, glands also enter the vulvar vestibule, usually as paired gland openings adjacent to and posterolateral to the urethra. These glands, with their ducts, are up to 1.5 cm in length. Skene glands are analogous to the male prostate gland. The minor vestibular glands are simple, tubular, superficial glands within the submucosa that have a maximum depth of 2.27 mm. They have a mucus-secreting columnar epithelium lining, without a defined ductal component, and enter directly to the mucosal surface of the vestibule. The glandular epithelium merges with the vestibular epithelium near the surface. The minor vestibular glands are analogous to the glands of Littre of the male urethra.

Vulvar vestibular papillomas (micropapillomatosis labialis), are small papillary structures usually under 3 mm in length, with a vascular core and nonkeratinized squamous mucosal epithelial surface. They may occur as small appendages of the external hymen or on the medial surfaces of the vulvar vestibule. They occur as single or multiple papillomas, and occasionally are clustered. They are a normal variant (1).

The labia minora are separated from the labia majora by the interlabial sulcus bilaterally. Anteriorly, the labia minora split to form the prepuce that hoods the clitoris, and the frenulum, which posteriorly fuses with the inferior portion of the clitoris. Posteriorly, the labia minora merge with the fourchette. The labia majora are bounded medially by the interlabial sulcus and laterally by the inguinal-gluteal folds. Anteriorly, the labia majora are bounded by the mons pubis and posteriorly by the perineal body. Within the perineal body and posteroinferior aspects of the labia majora, sebaceous glands are not associated with hair follicles. In these areas, these glands may be evident on physical examination, where they can be seen in some individuals as small, white spots referred to as Fordyce spots (14,27). Laterally, the skin of the labia majora has hair with skin appendages.

Lymphatic Drainage

The major lymphatic drainage of the vulva is to the femoral and inguinal lymph nodes. Lymphatic drainage from the anterior labia minora and clitoris is via channels that drain anteriorly and superiorly. These channels join the lymphatics draining the prepuce and labia majora, which then course laterally to the inguinal and femoral lymph nodes (18). The lymphatic drainage is predominantly ipsilateral, but contralateral drainage has been demonstrated in 67 percent of cases by Tc-colloid studies (13). The superficial inguinal lymph nodes receive most of the lymphatic drainage from the vulva and are the primary regional lymph nodes involved by metastatic tumor of the vulva. There are 8 to 32 superficial inguinal lymph nodes (median, 20 nodes), which include the superior and inferior node groups. The superior group is above the ligament of Poupart and the inferior group is between the ligament of Poupart and the junction of the saphenous vein and fascia lata (17).

Lymphatic drainage from both the clitoris and midline perineal area is bilateral (figs. 2-16–2-18). Additional lymphatic drainage from the clitoris is via the lymphatics draining the urethra and the dorsal vein of the clitoris. This pathway proceeds inferiorly to the symphysis pubis through the anogenital diaphragm to join the lymphatic plexus of the anterior bladder surface, draining into the interiliac and obturator nodes, or superiorly to the femoral and internal iliac nodes. A direct lymphatic pathway from the clitoris to the deep pelvic nodes has not been documented by in vivo colloid injection studies

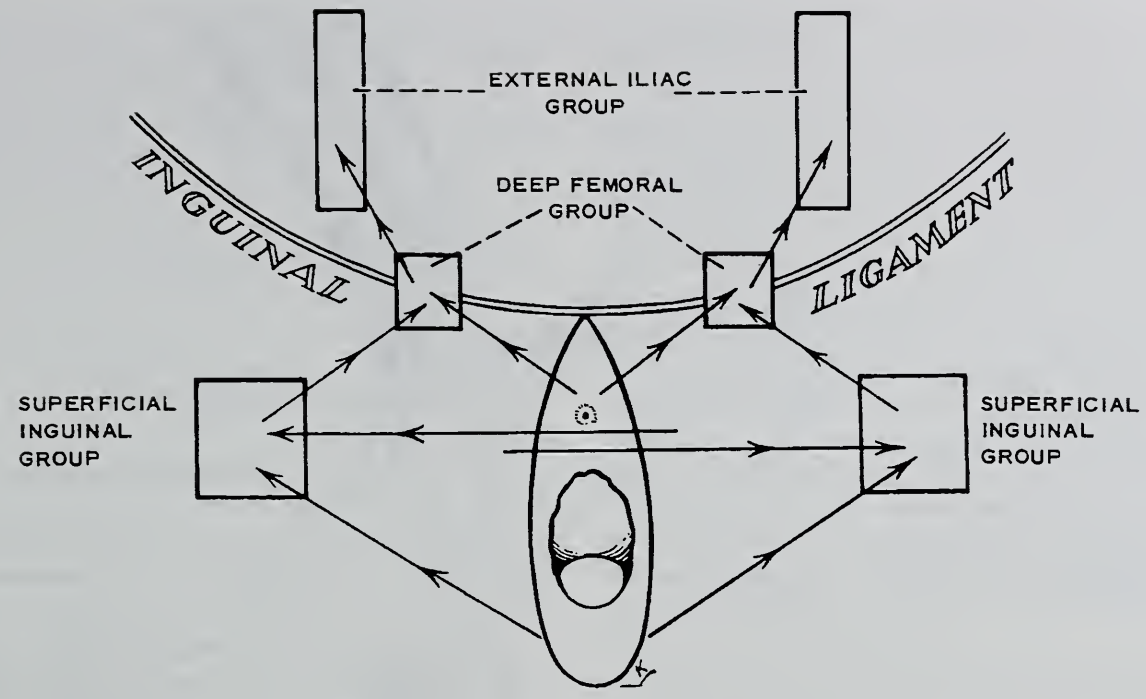


Figure 2-16

LYMPHATIC DRAINAGE OF THE VULVA

This schematic shows contralateral lymphatic drainage due to anastomoses of lymphatic vessels across the midline. (Fig. 3 from Way S. The anatomy of the lymphatic drainage of the vulva and its influence on the radical operation for carcinoma. Ann R Coll Surg Engl 1948;3:193.)

(13). In addition, clitoral carcinomas have not been documented to metastasize directly to deep pelvic nodes. Like carcinomas of the vulva arising in other anterior sites, clitoral carcinomas metastasize first to superficial inguinal nodes.

Microscopic Anatomy

The vulva, other than the vestibule, is covered by keratinized stratified squamous epithelium. The vulvar epithelium includes neuroendocrine cells, Langerhans cells, and lymphocytes (3,5). The epithelium of the vestibule is nonkeratinized stratified squamous epithelium that becomes rich in glycogen under the influence of estrogen. The epithelium responds to estrogen therapy like the epithelium of the vagina. The stratum corneum of the glycogenated nonkeratinized areas permits transudation of fluid through the epithelium, adding to the secretion of the apocrine, eccrine, and sebaceous glands. Keratinization is minimal on the frenulum and prepuce, but progressively increases peripherally, blending with the more heavily keratinized skin of the mons pubis, perineum, and surrounding skin.

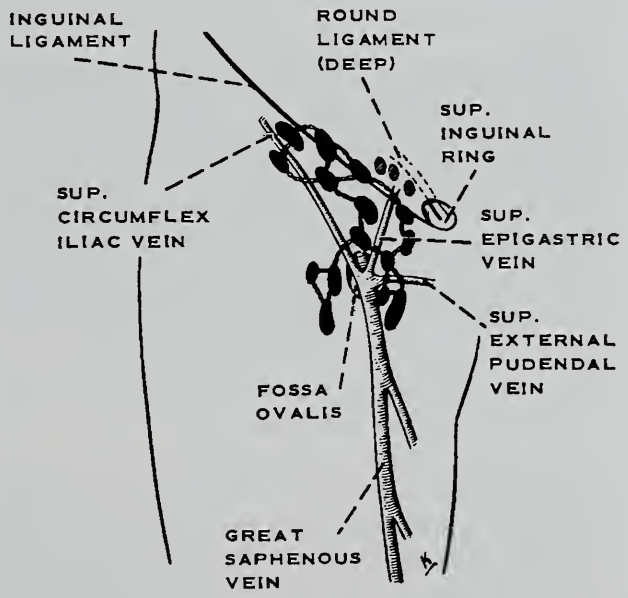


Figure 2-17

LYMPHATIC DRAINAGE OF THE VULVA

Lymphatic drainage of the vulva is illustrated in this schematic. (Fig. 1 from Way S. The anatomy of the lymphatic drainage of the vulva and its influence on the radical operation for carcinoma. Ann R Coll Surg Engl 1948;3:189.)

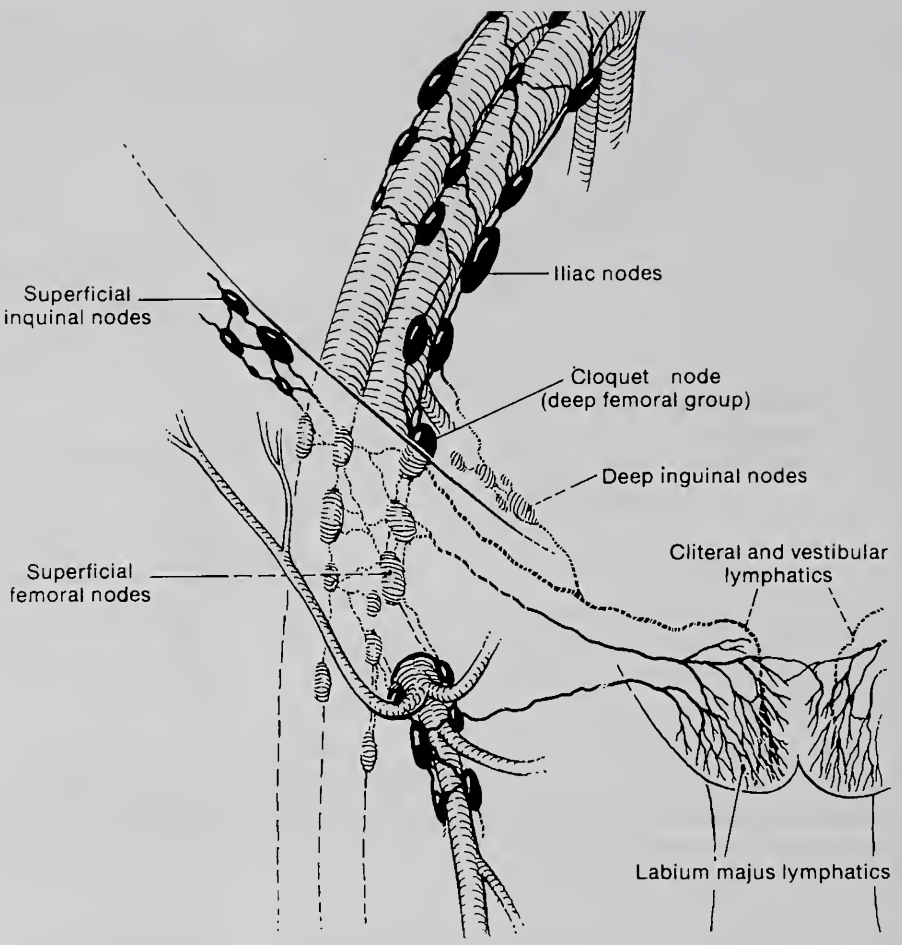


Figure 2-18

LYMPHATIC DRAINAGE OF THE VULVA

This schematic illustrates a fine and diffuse network of lymphatics. Fig. 14-4 from Schmidt WA. Principles and techniques of surgical pathology. Menlo Park, CA: Addison-Wesley; 1983:422.)

The vulvar epithelium beyond the vestibule is rich in melanocytes and Langerhans cells, and Merkel cells are also present. Peripheral to the vulvar vestibule, within the keratinized epithelium of the vulva, the melanocyte: keratinocyte ratio varies from 1:5 to 1:10 (12). There are 18.7 Langerhans cells per 100 keratinocytes within the vulvar epithelium (3). Merkel cells are neuroendocrine cells that are recognized within the vulvar epithelium, and in rare cases give rise to Merkel cell tumors (2).

The clitoris has a stratified squamous epithelial surface without gland elements. The submucosa is composed predominantly of erectile tissue that is contiguous with the bilateral conjoined corpora cavernosa. The latter branch at the base of the clitoris and extend inferiorly to the pubic rami.

The labia minora are rich in blood vessels and elastic fibers, but, unlike the labia majora, lack fat or smooth muscle. The epithelium of the labia minora is stratified squamous epithelium that is nonkeratinized on the most medial aspect, where it forms a portion of the vulvar vestibule, and thinly keratinized beyond the vestibule. The epithelium of the labia minora is usually devoid of skin appendages or glands although sebaceous glands are found in the most lateral posterior aspect of the labia minora in some cases.

Within the epithelium of the labia majora and perineum peripheral to the vestibular line of Hart, apocrine and sebaceous glands develop at the menarche. Sebaceous and apocrine glands develop without hair follicles in the medial portions of the labia majora and become mixed with hair follicles in the lateral portions. Medially, the skin of the labia majora contains sebaceous glands that open directly to the surface, without hair follicles. This relationship of sebaceous glands to the overlying epithelium is also found in the epithelium of the perineal body (14,27). Laterally, the skin of the labia majora has sebaceous glands with hair follicles.

The vestibular squamous epithelium merges with transitional type epithelium at the distal urethra and at the orifices of the Skene and Bartholin ducts. At the orifices of the minor

vestibular glands, the transition is from stratified squamous epithelium to mucin-secreting columnar epithelium, with metaplastic squamous epithelium seen at the glandular-epithelial junction in adults (21).

The apocrine glands within the vulva, like the axillary apocrine glands, begin their secretory function at the menarche. The eccrine sweat glands, however, function throughout life. The Bartholin glands are the major vestibular glands. They are tubuloalveolar glands with racemose architecture. The acini are lined by simple columnar, mucin-secreting epithelium. These acini empty into the Bartholin duct. The duct is approximately 2.5 cm in length and is lined predominantly by transitional type epithelium. The Bartholin duct is initially lined by mucinous columnar epithelium as it arises from the glands. This epithelium merges with transitional type epithelium that, more distally, merges with the nonkeratinized stratified squamous epithelium of the distal duct. The distal duct epithelium merges with the vulvar vestibule epithelium. The Bartholin ducts enter the vestibule bilaterally, posterolateral to the hymen. The paraurethral glands of Skene are distributed throughout the posterior and lateral aspects of the urethra and often have additional bilateral openings adjacent to and inferolateral to the external urethral orifice. They are lined by pseudostratified mucus-secreting columnar epithelium. The Skene gland ducts are lined by transitional type epithelium that distally is replaced with the nonkeratinized stratified squamous epithelium like that of the vestibule. These periurethral glands are the homologue of the male prostate gland and express both prostatic acid phosphatase and prostate-specific antigen (20).

The minor vestibular glands are simple glands lined by mucin-secreting epithelium. They are found within the vestibular epithelium, about the urethral meatus, throughout the vestibule, and within the proximal portions of the frenulum. Mucus-secreting columnar epithelium lines these glands except superficially where they become lined by nonkeratinized stratified squamous epithelium as they merge with the epithelium of the vestibule. Minor vestibular glands are identified in half to three quarters of vulvar vestibulectomy specimens (21,22). The glands undergo squamous metaplasia, similar to the endocervix. When this metaplastic epithelium completely replaces the glandular epithelium, a squamous mucosal, epithelial-lined vestibular cleft results (21).

Specialized anogenital glands of the interlabial sulcus are found between the labia majus and minus and are mammary like. They are lined by cuboidal to columnar epithelium and an underlying myoepithelium. The glandular luminal epithelial cells are apocrine type, with visible "snouts." These cells are immunoreactive for low molecular weight keratin as well as human milk-fat globule protein. Individual cells are also immunoreactive for carcinoembryonic antigen and S-100 antigen. Estrogen and progesterone receptors have been detected in these cells. There is evidence that these specialized anogenital glands are the origin of fibroadenomas, hidradenoma papilliferum, "milk cysts," and tissue previously interpreted as ectopic breast tissue that have been described in the vulva (25).

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3 HUMAN PAPILLOMAVIRUS: BIOLOGY AND CLINICAL IMPORTANCE

CLASSIFICATION AND PHYLOGENY

Papillomaviruses are a distinct taxonomic family of small epitheliotropic DNA viruses that infect mammals and birds (40). Papillomaviruses were previously considered members of the family Papovaviridae, but were removed once it was recognized that the size, organization, and sequence of the papillomavirus genomes differ substantially from those of other family members. Although papillomaviruses have been classified in more typical microbiologic terms into genera and species, human papillomaviruses (HPV) have historically been discussed as mucosal or cutaneous (based on site of infection), and then further divided into types, subtypes, and variants. The use of phylogenetic trees to demonstrate the degree of DNA sequence homology between HPV types has become an important research tool for understanding HPV biology and evolution. Clinically, HPV types may be considered oncogenic (capable of causing carcinoma) or nononcogenic (agents that produce exophytic warts and flat cervical intraepithelial neoplasia [CIN] lesions, but rarely carcinoma).

Over 100 HPV types have been identified and the number of recognized types is increasing. HPV typing is based on the sequence of the *L1* gene, which is highly conserved for each specific type. HPVs in which the open reading frame of the major capsid protein L1 demonstrates less than 90 percent sequence homology with existing types are considered to represent novel types and are numbered sequentially in order of discovery. Viruses that are identical in 90 to 98 percent of these sequences are designated as subtypes, and variants display even greater genetic identity with parent types. Emerging data suggest that variants may differ substantially in biologic behavior, which could ultimately have important clinical relevance.

A measure of the success of HPVs as pathogens is that they have attained remarkable type diversity with relatively stable genetic sequences. In part, this success may reflect the tendency of productive HPV infections to occur at epithelial surfaces, which allows most newly synthesized virions to be shed into the environment (192). Viral shedding into the vagina shields the virus from the host immune system, enhances the likelihood of transmission, and may reduce selection pressure on the virus, contributing to genetic stability over time.

Structure and General Organization of the Papillomavirus Genome

Papillomaviruses are nonenveloped organisms measuring approximately 55 nm in diameter. They contain a single genome of covalently closed, double-stranded, circular DNA consisting of about 8,000 base pairs (49,175,191,192). The viruses have an icosahedral capsid (protein shell) composed of a major protein, L1 (about 90 percent of capsid protein) and a minor protein, L2. Viral DNA is also associated with host histone proteins.

The genome of most HPV types has a common blueprint that includes at least eight open reading frames (potentially transcribed regions) (fig. 3-1) (32,43,105,116,158). Coding regions are limited to one DNA strand. The genome consists of three regions: 1) a noncoding long-controlling region (LCR), also referred to as the upstream regulatory region (URR); 2) an early region (containing the *E1, E2, E4, E5, E6*, and *E7* genes); and 3) a late region (containing the *L1* and *L2* genes). The designations "early" and "late" generally (but imperfectly) reflect the critical periods of the HPV life cycle when these genes are expressed. Early genes are involved in transcription and replication of HPV DNA and transformation of host cells, whereas late genes code for HPV structural proteins.

The HPV genome contains multiple promoters and codes for polycistronic RNA species that contain multiple open reading frames and translation initiation sequences. Regions of the genome that

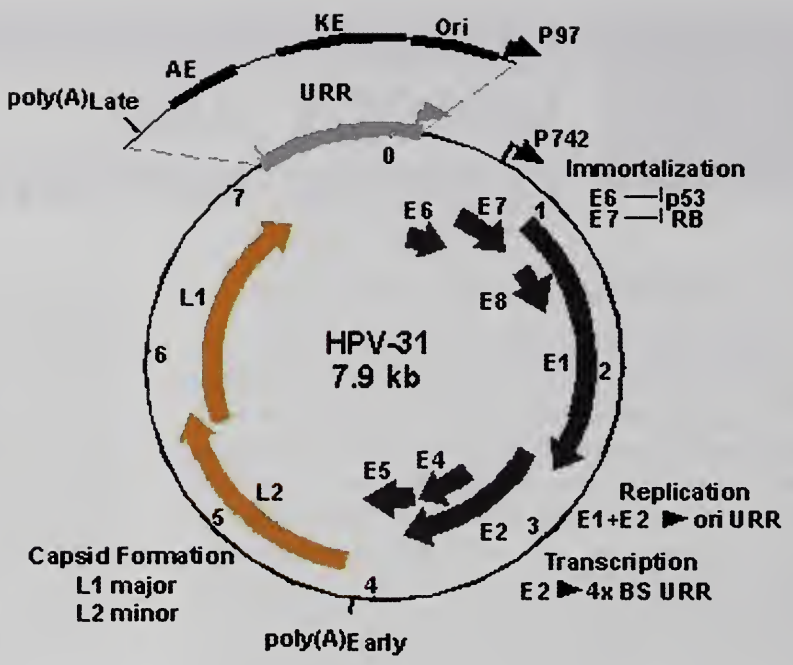

Figure 3-1

SCHEMATIC MAP OF THE CIRCULAR HUMAN PAPILLOMAVIRUS (HPV) GENOME

This map shows the location of the eight open reading frames and the effects of integration on viral sequences (see text). (Courtesy of Scott Terhune and Laimonis A. Laimins, Chicago, IL.)

are highly conserved between types have been exploited in the development of new assays capable of detecting multiple types.

The molecular pathogenesis of HPV-related disease is summarized in subsequent paragraphs that describe the structure of the HPV genome and its protein products. Conceptual models have been developed to describe the temporal and spatial expression of HPV genes during infection and their effects on cervical epithelium.

Long-Controlling Region (LCR)

The LCR varies significantly in length and sequence between HPV types. Sequence elements that are common to the LCR of all types include polyadenylation sites for mRNA of late genes, binding sites for E2 and E1, and the TATA box of E6 or E6/E7 promoters. When E2 binds to the LCR, it displaces transcription factors, downregulates the E6/E7 promoter, and upregulates HPV DNA replication mediated by the action of E1. The LCR also contains transcription enhancer sequences and binding sites for host transcription factors, including receptors for progesterone and glucocorticoids. The biologic importance of these receptor sequences is unknown, but the production of complete virions is linked to the maturation of the infected squamous epithelium, a process that is under the control of reproductive hormones. In addition, several putative risk factors (e.g., parity, oral contraceptives) for the progression of HPV infection to cancer precursors could be mediated by hormones.

Early Genes

The E1 protein functions as a DNA-dependent ATPase and an ATP-dependent helicase. E1 and E2 form a complex that promotes the stable binding of E1 to an AT-rich sequence at the origin of viral replication. E1 also associates with DNA polymerase alpha. E2 is a key regulator of viral replication and transcription. Evidence suggests that E2 binds to tubulin proteins (major components of the mitotic spindle) and mediates the physical partitioning of episomal HPV DNA (HPV DNA within host cell nuclei, but not physically integrated into the human genome) into daughter host cells during division (174).

The transcribed region of the *E4* gene overlaps with that of the *E2* gene, but *E4* is transcribed in a different reading frame. *E4* participates with *E1* in forming a fusion protein. In cutaneous infections, *E4* is involved in the formation of prominent nuclear and cytoplasmic inclusions; however, these are not characteristic of mucosal lesions. Although *E4* is classified as an "early gene," its expression is associated with the start of vegetative replication late in the viral life cycle. The actions of *E4* are incompletely understood, but the protein seems to bind to tonofilaments, disrupting the cellular cytoskeleton and interfering with normal keratinocyte maturation.

HPV Oncogenes: *E6* and *E7*

The E6 protein of oncogenic HPV types impedes the physiologic response of host cells to stress, specifically by blocking growth cycle arrest and apoptosis (105). E6 proteins contain approximately 150 amino acids, including the two zinc finger motifs that are required for its function. The E6 of oncogenic HPV types can interact with activated ras to transform rodent cells. High-risk E6 and E7 proteins can immortalize human keratinocytes; however, these cells cannot form tumors in nude mice without the cooperation of other oncogenes or extended passage. Experimental models mimic clinical infections in that HPV infection alone is inadequate for neoplastic transformation. Whereas transgenic mice expressing E7 develop benign differentiated tumors, mice expressing E6 develop malignant neoplasms. Additional studies have suggested that *E7* acts mainly as a promoter of carcinogenesis whereas *E6* plays a greater role in the progression of benign lesions to cancers.

The E6 protein of oncogenic types of HPV binds to the critical host cell cycle regulatory protein p53, leading to its degradation through a ubiquitin-dependent mechanism (182). This abrogates the p53-mediated cellular responses to DNA damage including growth arrest at the G1 to S transition and/or apoptosis (78). The function of E6 in oncogenic HPV infections is mediated by E6-associated protein (E6-AP), which functions as a ubiquitin ligase. E6 may also abolish p53-mediated repression of transcription through one of several possible mechanisms including the inhibition of p53 binding to DNA, interference with coactivators, or cytoplasmic sequestration. Interactions between E6 and myc and bak proteins may result in inhibition of apoptosis. Low-risk HPVs produce an E6 molecule that has relatively low affinity for p53 as compared to oncogenic HPVs, further supporting the designation of *E6* as an oncogene. Sustained activation of the cellular replication machinery may provide a means for HPV to replicate its own DNA and complete its life cycle.

Many protein families express E6-binding motifs, which may account for the protean effects of E6 on differentiation, immunity, and other processes (Table 3-1). Oncogenic E6 and E2 have antagonistic effects on p300/CBP, an important transcription coactivator. Interaction of the E6/E6-AP complex with the promoter of the catalytic subunit of the telomerase gene leads to its upregulation, allowing cells to avoid senescence. Independent of p53 binding, E6 may also produce carcinogenic effects such as promoting proliferation, inhibiting apoptosis, interacting with human proteins involved in adhesion, and maintaining cellular polarity and normal tissue organization. Although the intracellular quantity of E6 molecules is low relative to its multiple putative targets, it is hypothesized that merely by reducing levels of some intracellular molecules, E6 may drive carcinogenesis. Alternatively, the potent carcinogenic effects of E6 may reflect its expression at critical periods of the cell cycle. E6 protein is expressed in essentially all HPV-related lesions, making it attractive as a therapeutic target, and suggesting that restoration of p53 function may lead to growth arrest or apoptosis.

The E7 protein of oncogenic HPV types is structurally and functionally similar to oncoproteins of two other oncogenic HPV DNA viruses, E1A of adenovirus and the large tumor antigen of SV40 (78). E7 is a small acidic phosphoprotein composed of approximately 100 amino acids, including a zinc-binding domain with homology to a region of E6, which has prompted the speculation that E6 and E7 evolved from a common molecule. E7 has a short half-life and is present at low concentrations within cells. The main oncogenic effect of E7 is that it uncouples the normal linkage between differentiation and exit from the cell cycle, thereby allowing maturation and cell cycling to proceed concurrently. HPV uses the cell cycling machinery for its own replication; epithelial maturation is required for completion of the viral life cycle.

The oncogenic effect of E7 protein is mediated through its binding to the retinoblastoma (Rb) gene product and related "pocket proteins," so named because of the presence of pockets that bind viral oncoproteins and members of the E2F family of transcription factors (44,62). When E2F is not complexed to Rb family proteins, E2F may bind to another protein, DP; the resulting E2F-DP dimers bind to DNA and activate transcription. When E2F is linked to Rb family proteins, E2F-DP complexes repress transcription and block entry into S phase. Under physiologic conditions, the formation of E2F-Rb family protein complexes

Table 3-1

HUMAN PAPILLOMAVIRUS (HPV) E6 AND E7 ONCOPROTEINS: SUMMARY OF DIVERSE INTERACTIONS WITH HOST PROTEINS AND MAJOR EFFECTS[a]

HPV Oncoproteins	Human Host Proteins	Functions of HPV Oncoproteins
E6	p53	Cell immortalization
	E6-associated protein (E6-AP)	p53 degradation (via binding to E6-AP)
	ERC55	Antiapoptotic effect
	HDLG	Destabilization of chromosomes
	Paxillin	Enhancement of foreign DNA integration and mutagenicity
	Interferon regulatory factor 3	
	Bak	Activation of telomerase
	E6TP1	Blockade of interferon
E7	Retinoblastoma (Rb)	Cell immortalization
	Rb-related pocket	Activation of cyclins E and A
	E2F/cyclin A complex	Inactivation of Rb-related pocket proteins
	Histone H1 kinase	Induction of apoptosis
	TATA box-binding	Inhibition of cyclin-dependent kinase inhibitors (p21, p27)
	Cyclin E	
	Subunit 4 (S4) adenosine triphosphate	Enhancement of foreign DNA integration and mutagenicity
	C-jun	
	hTid-1	Degradation of tyrosine kinase Blk (?)
	Mi2 (histone deacetylase complex)	
	M2-pyruvate kinase	
	p48	

[a]Adapted from reference 192.

is tightly linked to phosphorylation of Rb family proteins. During cell cycling, phosphorylated Rb permits E2F to activate transcription, whereas in G0, Rb is not phosphorylated and E2F-mediated transcription is inhibited.

In oncogenic HPV infections, E7 protein overrides physiologic control mechanisms by binding to Rb and related proteins, leading to dissociation of E2F-Rb family complexes and promoting proteolytic degradation of pocket proteins (Table 3-1). In turn, this leads to the E2F-mediated transcription of key molecules required for cell division, including DNA polymerase alpha, enzymes involved in nucleotide biosynthesis, and cyclins that control progression through S phase. Despite recent advances in the molecular pathogenesis of cervical neoplasia, the relationship between E7-induced transcription of E2F-controlled genes and transformation remain incompletely understood.

E7 also induces resistance to the growth inhibitory functions of transforming growth factor-beta (TGFβ). Loss of TGFβ growth inhibition seems to emerge in concert with reduced responsiveness to differentiating signals, and may be mediated through the effects of E7 on either p21 and p27 or the pocket proteins. Similarly, E7-infected cells do not respond normally to tumor necrosis factor-alpha (TNFα) with the expected combination of G1 arrest and differentiation. E7 interferes with the cytostatic signals produced by interferons, which are synthesized by cells in response to viral infections, and reduces levels of insulin growth factor binding protein 3 (potentially increasing access to unbound growth factors).

Expression of E6 and E7 is associated with increased production of centrioles, the precursors of centrosomes, which form the polar bodies of the mitotic spindle. Normally, replication of centrosomes is tightly linked to cellular replication. The effect of E7 on centrosomes, in particular, may represent an important cause of genetic instability.

The Putative Oncogene *E5*

Studies of bovine papillomaviruses (BPV) have provided most of our knowledge about *E5*. E5 is a small transforming, hydrophobic membrane protein that seems to function by activating growth factor receptors (e.g., platelet-derived growth factor [PDGF]-beta receptor) and interacting with vacuolar ATPase function (43). By inhibiting vacuolar ATPase, BPV E5 prevents acidification of Golgi

bodies, which in turn may alter the final packaging of molecules, including growth factor receptors, and could affect their function.

HPV E5 is only weakly transforming and differs in length and sequence from BPV E5. Like BPV E5, HPV E5 localizes to organelle membranes, including the membranes of the endoplasmic reticulum, Golgi body, and nucleus. HPV 16 E5 induces anchorage-independent growth, reduces the minimal serum requirement for growth, produces transformation of mouse fibroblasts, and stimulates DNA synthesis in human keratinocytes. Rather than activating PDGF receptor-beta, HPV E5 seems to promote growth by reducing the metabolism of the epidermal growth factor (EGF) receptor. In addition to increasing responsiveness to EGF, HPV E5 may increase DNA synthesis in response to endothelin-1 and repress expression of the cell cycle inhibitor p21. HPV E5 also interacts with vacuolar ATPase, possibly inhibiting acidification of the Golgi, transmembrane transport of molecules into the Golgi, and intercellular signaling. It is postulated that decreased acidification of the Golgi may inhibit degradation of EGF receptor, which is often strongly expressed on cervical cancer cells. Integration of the HPV genome into the human host genome often leads to loss of the *E5* gene, suggesting that if *E5* plays a role in the pathogenesis of cervical cancer, it must act at an early stage.

Late Genes

The late genes code for the structural capsid proteins L1 and L2. In vitro, L1 assembles into virus-like particles (VLPs), morphologically similar to virions, a feature that has been exploited in vaccine development (see below). When L1 and L2 are coexpressed in vitro, both proteins are incorporated into VLPs. L2 may by required for encapsidation of HPV DNA.

In Vitro Models of HPV Infection

When HPV 11-infected human foreskin is engrafted under the renal capsule of athymic mice, it forms cysts with a lining resembling condylomata (88). HPV 16 virions have been obtained by implanting a cell line derived from CIN in mice with severe combined immunodeficiency (SCID) (11). Virions are also derived from raft cell cultures in which keratinocytes are grown on plugs of collagen at an air-liquid interface (28). The oncogenic HPV types 16, 18, 31, and 33, but not the low-risk types 6 and 11, are capable of immortalizing human foreskin or cervical keratinocytes (49). Full transformation, however, requires expression of both E6 and E7 and an activated *ras* gene. HPV immortalized keratinocytes do not mature normally in raft cultures, and with repeated passage, may acquire properties of anchorage-independent growth and tumorigenicity in mice.

HPV Life Cycle: General Aspects

HPV may produce productive or vegetative infections that generate abundant new infectious virions or abortive infections that produce few virions, but may lead to cervical neoplasia. Some evidence suggests that HPV also assumes a latent state in which the virus persists within tissue, but neither actively replicates nor transforms the host epithelium; the existence of latent HPV infections is unproven, however. The biology of different patterns of infection is tightly linked to the development of cervical pathology.

HPV infections presumably begin at the transformation zone (squamocolumnar junction), which is the site where most CIN lesions appear to develop. The reason why HPV has a predilection for this particular anatomic site is unknown. Simplistically, viral access to target cells may be facilitated by thinning of the epithelium at the squamocolumnar junction. Additional possible factors include local immunologic conditions, expression of cell surface receptors that favor HPV binding and intracellular entry, and the presence of replicating stem cells that do not mature, which could provide a stable microenvironment suitable for long-term persistence.

It is presumed that HPV passes through defects in the epithelial surface to reach the basal cell layer. It has been postulated that heparan mediates an initial interaction between HPV and host cell membranes, followed by binding to a receptor complex and internalization (56). The integrin alpha-six beta-four protein complex has been proposed as a possible receptor for HPV (46), but this has not been established. It has also not been determined whether the ability of HPV to successfully infect specific cells is governed by receptor expression or the ability of the virus to usurp the internal cellular machinery. It is

thought that infection begins in stem cells and possibly, transit-amplifying cells, which also have some capacity to divide (158,163).

HPV Life Cycle: Productive (Vegetative) Infections

Productive HPV infections require maturing squamous epithelium as a substrate. In normal uninfected cervical mucosa, maturation proceeds as cells migrate toward the epithelial surface in conjunction with cell cycle arrest. Productive HPV infections create a pathologic condition in which maturation proceeds but replication continues, which means that the metabolic machinery of the dividing cells is available to the virus (18,163). HPV seems to achieve this effect through inactivation of the cell cycle inhibitors p21 and p27.

Tissue culture studies suggest that episomal (nonintegrated) HPV DNA replicates within basal cells until 50 to 100 viral DNA copies are formed (163). In basal cells, HPV replication is tightly controlled by E2, which interacts with the early promoter to repress transcription. In this model, one epithelial cell resulting from cell division migrates superficially and undergoes differentiation, whereas the other cell remains in the basal region, providing a renewable source of viral DNA. Basal cells are protected from damage; HPV cannot complete its life cycle in these undifferentiated cells. Whereas uninfected maturing spinous cells exit the cell cycle, HPV-infected cells continue to cycle under the influence of the HPV oncoproteins E6 and E7. The uncoupling of division and maturation permits viral replication and full particle assembly. The reason why maturation is required for transcription of late genes is unknown, but may reflect the action of differentiation-specific transcription factors. Differentiation is associated with a switch in control of transcription from the early promoter to the late promoter, which is not repressed by E2. It is thought that promoter switching relaxes controls on viral replication, leading to high copy number.

HPV Life Cycle: Abortive Infections

The factors that convert productive infections to abortive infections represent a central question in HPV research; fundamentally, this switch converts an infectious process to a neoplastic one. In abortive infections, expression of late genes and virion assembly are inhibited, permitting the increased epithelial thickening characteristic of CIN 3. Morphologic features indicative of cellular maturation (cytoplasmic enlargement and nuclear condensation) and characteristics of vegetative infections (expression of E4 and L1 and production of whole virions) are limited to small foci present at the epithelial surface. Instead, the full thickness of the epithelium consists of immature-appearing cells that express HPV E6 and E7 and the host genes that they induce (Ki-67, PCNA, minichromosome maintenance proteins, and other markers of cell cycling) (fig. 3-2).

Persistent HPV infection in the context of CIN 3 over a period lasting 10 to 20 years provides conditions that permit the development of invasive carcinoma. High levels of E6 and E7 likely contribute to progression by promoting cell cycling and genetic instability. Furthermore, in some CIN lesions and in most cancers, HPV DNA is physically integrated into the host chromosome (34,181). Based on a review of 192 cases, Wentzensen et al. (181) concluded that the distribution of specific integration sites within the human genome is random; however, there is a strong predilection for fragile sites (regions prone to chromosomal breakage), allowing integration of foreign DNA. It is postulated that genetic instability produced by E6 and E7 and the cellular repair process that is evoked may increase the risk of HPV integration. In this view, the carcinogenic effects of integration are related mainly to its effects on expression of HPV genes rather than on human genes. For example, integration may lead to loss of E1 and E2 function, leading to overproduction of the oncoproteins E6 and E7.

HPV Life Cycle: Latency

It has been proposed that HPV infection may assume a latent state characterized by the absence of differentiation-dependent production of whole virions (19,126,163). Two observations support the latency concept: 1) immunosuppressed patients often test positive for multiple HPV types, including types that are uncommon in the general population, and 2) laryngeal papillomas often recur repeatedly over many years. In both of these instances, productive infections follow prolonged periods of normalcy without

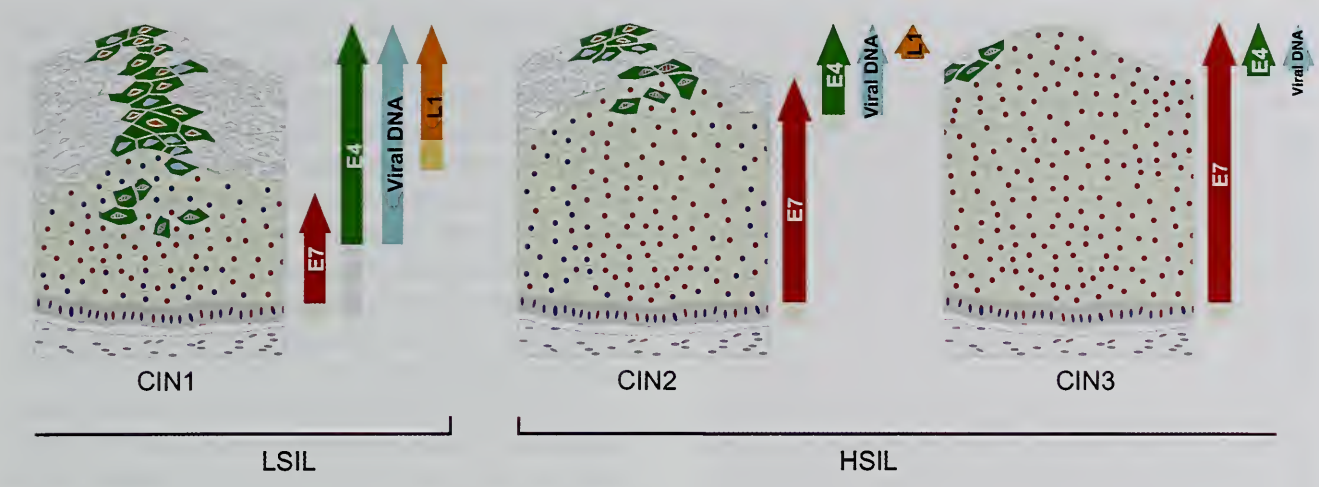

Figure 3-2

SEQUENTIAL EXPRESSION PATTERN OF SELECTED HPV GENES AND HPV DNA CONTENT

This drawing displays the sequential expression pattern of selected HPV genes and HPV DNA content within cells as they ascend from the basement membrane to the surface. In cervical intraepithelial neoplasia (CIN) lesions of varying grades, the sequential patterns are similar but the spatial distribution and extent differ. In CIN1, the archetype of a vegetative infection, expression of E7 is restricted to the base, whereas E4 expression, HPV DNA amplification, and finally L1 expression begin in the lower spinous layers. In CIN3, the most proximate cancer precursor, E7 expression predominates, expression of E4 and L1 are limited to small superficial foci, and the number of HPV DNA copies is limited. Red nuclei = E7 expression; dark blue nuclei = nonpermissive cells; green cytoplasm = E4 expression; orange nuclei = L1 expression; turquoise nuclei = amplified HPV DNA; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion. (Adapted from Middleton K, Peh W, Southern S, et al. Organization of human papillomavirus productive cycle during neoplastic progression provides a basis for selection of diagnostic markers. J Virol 2003;77:10195.)

evidence of new viral exposure. In this model, recrudescent laryngeal papillomas and new cervical lesions in immunosuppressed patients are interpreted as reactivation of latent HPV rather than as acquisition of new infection.

In response to HPV infection, host cells activate both intracellular and intercellular regulatory mechanisms to suppress the function of viral oncogenes. For example, studies have found that cells may undergo senescence despite the continued transcription of E6 and E7. It has been postulated that phosphorylation or dephosphorylation of oncoproteins or increased synthesis of cyclin-dependent kinase inhibitors plays a role in this process. The function of multiple cytokines may also affect transcription of E6 and E7 (192). Several population-based epidemiologic studies show that the prevalence of HPV infection declines with increasing age until the fifth decade of life, then rises for a few years, and finally declines progressively to very low levels with increasing age (63). An explanation for this age-dependent pattern is lacking, but intracellular or intercellular regulatory mechanisms leading to recrudescence of latent infection could play a role.

HPV EPIDEMIOLOGY

Oncogenic HPV Types Cause Cervical Cancer

Data accumulated over the last decades of the 20th century have provided definitive proof that approximately 15 types of HPV cause nearly every cervical cancer worldwide (comprehensively reviewed in reference 14). This proof was made possible by technical advances in HPV DNA testing, improved criteria for evaluating cervical cytology and histopathology, and successful completion and analysis of large multidisciplinary studies. Evidence supporting the causal role of HPV in cervical carcinogenesis is summarized below.

HPV is strongly associated with cervical cancer. The International Agency for Research on Cancer (IARC) multicenter case-control study (14) found the odds ratio (OR) for cervical cancer associated with HPV DNA to be 50 to 100. ORs for HPV 16 and squamous cancer and HPV 18 and adenocarcinoma were between 100 and 900 in different countries (Table 3-2). HPV infection was associated with approximately 95 percent of the cancers included in this large

Table 3-2

PREVALENCE OF COMMON HUMAN PAPILLOMAVIRUS (HPV) TYPES IN CERVICAL CANCER AND RISK OF CANCER ASSOCIATED WITH INFECTION: DATA FROM THE IARC MULTICENTER CASE CONTROL STUDY[a,b]

HPV	Prevalence (%) in Cases	Prevalence (%) in Controls	Odds Ratio
HPV 16	59	30.3	182
HPV 18	12	8.2	231
HPV 45	5	3.9	148
HPV 31	4	4.8	72

[a]Data from IARC multicenter case control study for 1545 cases with single HPV infections. (Adapted from Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002;55:244-65.)

[b]IARC = International Agency for Research on Cancer.

investigation. Cumulatively, HPV types 16, 18, 31, and 45 accounted for approximately 80 percent of cancers associated with single infections. HPV types 31, 33, 35, 45, 51, 52, 58, and 59 were also demonstrated to represent carcinogens. Although multiple infections were more common in women with cancer, this was not associated with increased cancer risk. Data from the IARC study are consistent with results from a large body of amassed literature from all regions of the world. Risk factors and HPV detection in women with CIN 3 and cancer seem similar. The strength and consistency of the relationship between oncogenic HPV types and cancers provide strong evidence of causality.

Specificity of association is considered a minor criterion for assessing causality. Among HPV infections, certain specific relationships have been consistently determined. Foremost, cancers are related to about 15 oncogenic types, but not to nononcogenic types. HPV 16 and related viruses predominate in cervical squamous carcinomas and HPV 16 alone accounts for about 80 percent of HPV-related vulvar cancers. In contrast, HPV 18 and phylogenetically related viruses account for a relatively higher percentage of cervical adenocarcinoma and adenosquamous carcinoma compared with squamous cell carcinoma (14,15,117,176). Therefore, relationships between HPV types and specific histologic types of cancer are not random.

Establishing temporality is critical for proving causality: exposure to a causal factor must precede the disease that it produces. Evidence that HPV infection precedes and predicts the future development of cervical neoplasia is strong. Descriptive data show that the peak incidence of cervical HPV infection occurs among women under age 30 years, whereas the peak incidence of cancer in the United States occurs in the fifth decade (180). Furthermore, cohort studies have demonstrated that oncogenic HPV infection is associated with substantial risk for the future development of disease (96,139,148,177,185,188). In a study of 20,000 participants undergoing routine cervical screening, women with a single positive baseline HPV test were 18 times more likely than those with a negative test to receive a diagnosis of CIN 3 or cancer within 45 months. Among women who tested positive, CIN 3 or cancer was identified in 6.9 percent within 10 years (148). For many years, cervical cancer risk has been linked to sexual behavior; however, epidemiologic studies have conclusively demonstrated that sexual activity functions as a risk factor for viral acquisition (141), which in turn precedes the development of disease.

Demonstration of a biologic gradient or dose response effect is considered another sign of causality. Assessment of viral load in lesions is technically difficult and not analogous to measuring exposure to toxins or drugs. Nonetheless, data have consistently found that biopsy-proven disease is associated with a higher viral load than subclinical infection (cytologically normal) (149) and some studies have suggested that high loads of HPV 16 are associated with an increased future risk of neoplasia (76,189).

Abundant experimental and mechanistic data support the biologic plausibility of HPV as a cancer-inducing agent. HPV is capable of immortalizing and transforming cells in culture and the effects of E6, E7, and to a lesser degree, E5, promote carcinogenesis (see above). The oncogenic properties of HPV have been demonstrated in many animal models, including cattle, rabbits, and dogs. The totality of evidence that HPV causes most cervical cancers is overwhelming and irrefutable, and HPV has been recognized as such by numerous scientific bodies.

The epidemiology of CIN and cancer is most easily understood in terms of the effects that factors exert on the natural history of HPV infection including: 1) exposure/infection;

2) persistence/progression to a cancer precursor (roughly, CIN 3); and 3) development of invasion. A basic knowledge of HPV epidemiology has become essential for pathologists given its influence on clinical practice, including the use of HPV testing for clarifying atypical squamous cells of undetermined significance (ASC-US) cytology (155) and its role as an adjunct in primary screening (20,35,52,108,123), refinement of the Bethesda System for reporting cervical cytology (156), and formulation of evidence-based management guidelines (187).

The cervical cancer referred to in the following sections is squamous cell carcinoma, the numerically predominant histologic tumor type. Essential findings for adenocarcinoma are summarized in a separate section. Also, note that the broadly defined historical term "atypical squamous cells of undetermined significance" (ASC-US) has been replaced with the term "atypical squamous cells" (ASC), which is subdivided into "of undetermined significance" (ASC-US) and "cannot exclude high-grade squamous intraepithelial lesion (HSIL)" (ASC-H).

Acquisition and Prevalence of HPV

A link between sexual activity and cervical cancer has been recognized for many years, but proof that cervical cancer is caused by sexually transmitted HPV infection was not possible until sensitive methods for detecting HPV DNA were developed. Subsequently, studies demonstrated that girls who had not had intercourse invariably tested negative for HPV (4,47,80). In one report (80), among 100 virgins tested, all but 1 was negative for both HPV DNA and antibodies to HPV 16. One subject tested weakly positive for HPV 6, but she had reported some level of sexual contact without penetration.

Although sexual behavior is strongly linked to the risk of testing positive for HPV (8,53,95, 113,131,141,183), the frequency of occurrence and clinical relevance of vertical transmission have been debated. Rice et al. (135) estimated that perinatal transmission is extremely common (69 to 77 percent of births) and that 20 percent of children test positive when highly sensitive assays are used. This high frequency of infection could reflect massive exposure to HPV at birth, ascending infection following ruptured membranes, and horizontal transmission.

Proponents of the position that vertical transmission is rare have argued that HPV DNA testing may overestimate the prevalence of "infection," secondary to contamination of samples at collection or in the laboratory (42). In addition, positive serologic tests must be interpreted cautiously. Transplacental transport of maternal antibodies may result in positive tests among infants that do not reflect neonatal infection. Detection of serologic responses in children (approximately age 2 years) may reflect cross-reactivity with cutaneous HPV types associated with the emergence of skin warts at that age. Apart from the rare cases of laryngeal papillomatosis, the absence of antibody detection among virgins has also been offered as evidence against the clinical relevance of vertical transmission.

Case-control and cohort studies have established the main risk factors for HPV DNA acquisition. Among girls and young women, the estimated cumulative incidence of HPV infection after 24 to 36 months of follow-up ranges from about 39 to 55 percent (53,68,113,183), mainly reflecting infections with oncogenic types. Sexual behavior, variously assessed as cumulative, new or recent sexual partners, is the main determinant of incident (new) HPV detection. In one report, incident infections were equally common among virginal and sexually active college-aged women (183). Nonpenetrative sexual contact was associated with HPV detection among virgins but not among experienced women. In a study of teenagers, each new partner per month was associated with a 10-fold increased risk of incident HPV detection (113). The risk for HPV infection seems to plateau among women with many contacts, such as patients in sexually transmitted disease clinics and prostitutes (81).

A metaanalysis found that condom use may afford modest protection against external warts and possibly other cervical lesions, but a reduction in HPV DNA detection was found in only one of six studies (104). Given that users may have sporadic unprotected contacts and that condoms cannot fully cover all areas of infected skin and mucosa, these data are expected.

The detection of oncogenic HPV infections declines sharply with increasing age (73,109), which most likely reflects acquired immunity (21). In some populations, the sharp decline between the third and fourth decades is followed

by an increase in the fifth decade, although rates among the youngest women are always highest. Age-specific rate patterns for nononcogenic types of HPV are less clear. Franco et al. (53) found that the incidence of nononcogenic infections did not vary with age, but HPV prevalence was highest among the youngest women, possibly reflecting greater persistence in that age group. Kjaer et al. (82) found that the prevalence of nononcogenic HPV infections was related to the number of recent sexual partners, but not to age or lifetime number of partners, suggesting that the reduced persistence of nononcogenic types may increase the impact of recent exposure as a determinant of detection.

Conducting studies of sexual partners to understand the mechanisms of HPV transmission has proved challenging. HPV test results may be discordant if individuals have had multiple partners or if only one member of a pair has cleared the virus. In addition, collecting satisfactory specimens for HPV testing from men is difficult (51). Despite these limitations, it is clear that the sexual behavior of men is an important determinant of cervical cancer risk for their partners (13,118). This view is supported by the geographic clustering of cervical and penile cancers and the increased risk of cervical cancer among women whose partners have penile cancer, who have had a previous partner who died of cervical cancer, or who travel.

In Spain, a country that has low cervical cancer rates, a woman's risk of cervical cancer is elevated by the following characteristics among her partners: lifetime number of partners and contacts with prostitutes, early age at first intercourse, smoking, positive serology for *Chlamydia trachomatis*, and a history of oral or anal sex (13). Detection of oncogenic HPV DNA among men conferred a seven-fold risk of cervical cancer in their partners. Data for cervical cancer risk among monogamous women show similar relationships for their partners.

In contrast, data from Colombia, a country with high rates of cervical cancer in which men have more partners and contacts with prostitutes than in Spain, only lack of education and seropositivity for *C. trachomatis* among men increased the risk of cervical cancer in their partners (118). Data from Spain and Colombia suggest that in some countries with high cervical cancer rates, virtually all sexually active women are exposed to HPV. In these countries, acquisition of HPV is probably a much weaker determinant of cancer risk than factors associated with progression of HPV to cancer. An international study found that circumcision was associated with a reduced risk of HPV in penile samples and lowered risk of cervical cancer among women whose partners had multiple other contacts (23).

HPV Persistence and Progression

Although oncogenic HPV infections are extremely common among sexually active young women, approximately 70 percent of prevalent infections resolve within 1 year and perhaps 90 percent over a longer period. Given that persistence of oncogenic HPV infection is required for progression to a cervical cancer precursor (68,69, 84,114,124,134,177,188), identifying the factors that influence such persistence is important.

Persistence studies pose difficult requirements: 1) identification of large stable cohorts that can be followed with repeated measurements for years; 2) costs for repeated HPV testing and typing; 3) difficulties in accurately assessing epidemiologic cofactors; and 4) accounting for the way in which treatment modifies the natural history of HPV infection. To date, a widely accepted definition of persistence has not been developed; repeated detection of the same HPV type is common to all criteria, but minimum duration, assay sensitivity, and analytical considerations vary among researchers. Despite the use of different definitions of persistence between studies, a meta-analysis of 41 investigations found that HPV persistence was clearly related to cervical cancer precursors and cancer. However, the magnitude of risk varied widely (79a). Many women with persistent HPV infections have repeatedly abnormal cytology, leading to treatment for minor lesions, which prevents accurate assessment of the risk for progression to CIN 3. In addition, HPV type-specific persistence and progression to CIN 3 are identified concurrently, which makes separating risk factors for these two processes challenging. Based on a statistical model, Meyers et al. (120) concluded that the incidence of HPV infection and its rate of progression to high-grade lesions produce the greatest impact on the incidence of age-specific cervical cancer.

The course of HPV infections reflects the properties of the specific viruses, the characteristics of the human hosts, the effects of exogenous exposures, and the interaction of these conditions over time. Despite the enormous complexity inherent in addressing this subject, this process is now partly understood.

Oncogenic HPV types, particularly HPV 16, are more likely to persist than low-risk types (66,68,84). Furthermore, intratypic sequence variants of HPV 16, and possibly, HPV 18 (catalogued by geographic source), may confer different risks for cervical cancer. Non-European variants of HPV 16 in particular are associated with a higher risk for cervical neoplasia than European variants, although the latter also confer considerable cancer risk (178). Further work on this topic is needed.

The role of *elevated viral load* (HPV content in samples obtained from infected women) in predicting the persistence and progression of infection has been debated. Although women with biopsy proven lesions generally have higher HPV loads than women with clinically occult infections (149), the range of load within each grade of CIN is highly variable and overlaps, limiting the clinical utility of load as a prognostic marker (149,165). Several studies have found that higher loads of HPV 16 specifically are more often associated with prevalent high-grade CIN (37,165) and limited data suggest that high loads of HPV 16 are associated with increased risk for the development of high-grade CIN subsequently in follow-up (189). Although studies suggest that women with prevalent HPV infections are more likely to acquire new infections, the presence of one HPV type does not seem to influence the risk of persistence, a more specific marker of risk for cervical neoplasia (97,138). In addition, the state of the virus (integrated into human host DNA versus episomal), methylation status of the virus, and transcript levels of the oncogenes *E6* and *E7* may also be associated with risk of persistence and subsequent neoplasia, but further studies are required.

Host genetics and immune status are two key factors that are likely to predict the outcome of HPV infections. Human leukocyte antigens (HLA) are important determinants of the efficiency of antigen presentation to immune effector cells and, therefore, may influence the outcome of HPV infections. A protective association with HLA DRB1*13 and/or DQB1*603 has been reported consistently, whereas specific HLA class II markers of increased risk have not been identified (67). Risk associations for polymorphic variants of HLA class I antigens are sparse. A protective association with HLA C*0202 was reported in an analysis combining data from three diverse populations (179). Whereas humoral immunity may play a role in preventing HPV infection, elimination of an existing infection seems more closely related to an effective cellular immune response (86,102,186). Variation in receptor variants on natural killer cells may be an important source of genetically influenced risk, but this topic has not been adequately explored, in part because the required assays are technically challenging.

Impaired cellular immunity attributable to human immunodeficiency virus (HIV) infection, transplantation, or immunosuppressive drugs increases HPV persistence, development of genital warts, CIN, and cervical cancer (127,130,164,186). Deficiencies of humoral immunity, however, do not seem to increase the risk for HPV-related diseases. The United States Center for Disease Control (CDC) has designated cervical cancer as an acquired immunodeficiency syndrome (AIDS)-defining illness among HIV-infected women. Women with AIDS have an excess risk of carcinoma in situ of the cervix (RR = 4.6) and vulva/vagina (RR = 3.9), with risk increasing with duration since HIV seroconversion (54). HIV infection is associated with a similarly elevated risk for invasive cancers at these sites, but HIV infection probably does not speed the transition from in situ to invasive disease. Highly active antiretroviral therapy (HAART) improves CD4 levels, but has not been associated with regression of cervical cancer precursors, suggesting that immunity may have a minimal effect on the final stages of carcinogenesis (126).

In a large cross-sectional study, HPV DNA was detected in 63 percent of HIV-positive women as compared to 30 percent of high-risk HIV-negative women (127). Patients with peripheral CD4 counts below 200/mm^3 were at the highest risk for HPV infection; above this CD4 level, high levels of HIV viral load represented an additional risk factor for HPV DNA detection. Both HIV-negative and HIV-

positive women were infected with a similarly broad range of HPV types, but multiple infections were three-fold more common among HIV-infected patients. Among HIV-positive women, HPV infection was associated with measures of lifetime HPV exposure but not recent exposures, suggesting that the higher prevalence of HPV among HIV-positive women reflects increased HPV persistence. Data from a cohort of high-risk women support this view: persistence was detected in 24 percent of HIV-positive women as compared to 4 percent of HIV-negative patients (164). The risk of new HPV infections was similar among HIV-positive and HIV-negative patients. A meta-analysis concluded that HIV infection increases the risk of CIN among women who are HPV positive (103).

Three exposures have received particular attention as possible factors related to HPV persistence and/or progression: *parity, smoking, and oral contraceptive use* (22,24). Multiparity has been associated with an increased risk of cervical neoplasia in multiple studies, including investigations in Costa Rica (65) and the IARC multicenter study (119). In the IARC study, seven or more full-term pregnancies are associated with nearly a four-fold risk for cervical cancer. The increased risk for cervical neoplasia associated with multiparity generally persists when analyses are restricted to HPV-infected women, indicating that the association most likely reflects a true increase in risk of HPV infection progressing to cervical cancer. Although some investigations have failed to identify an increased risk for multiparity (26,83), this may reflect a low frequency of multiparous women in these study populations (24).

The decline in cervical cancer in the United States during the early 20th century (prior to the implementation of screening) may reflect a *reduction in childbearing* (7). Possible mechanisms that account for the risk associated with parity include trauma during parturition, hormonal changes of pregnancy, pregnancy-related immunosuppression, and possibly, ectropion. In the Costa Rica study, a history of miscarriages, abortions, stillbirths, ectopic pregnancies, Cesarean sections, and age at first pregnancy were not associated with increased risk (65). Age at menarche and age at menopause were unrelated to increased risk in the IARC study (119).

The link between *smoking and cervical neoplasia* has been suspected since analyses of registry data revealed that rates of lung cancer among men and cervical cancer paralleled each other within geographic regions (184). A review of over 50 studies concluded that smoking increases the risk of cervical cancer among HPV-infected women, resulting in an approximate doubling of risk overall. The strongest effects were found among heavy smokers (166). A multivariate analysis of a large cohort followed for up to 10 years found that smoking a pack of cigarettes or more per day resulted in a four-fold increased risk for cervical neoplasia (26), and a similar relationship between heavy smoking and risk was found in another study (41). Szarewski et al. (166) reported that regression of photographically identified cervical lesions occurred in 82 percent of women who stopped or markedly reduced their smoking for 6 months as compared to 28 percent of those who continued to smoke. Among young women, data suggest that smokers maintain their HPV infections longer than nonsmokers and have a reduced probability of clearing oncogenic HPV types (58).

Multiple mechanisms could mediate the risk of cervical neoplasia associated with smoking (166). Cervical mucus contains nicotine, which can be converted to carcinogenic nitrosamines. In some studies, concentrations of nicotine in mucus have correlated with cigarette consumption and have exceeded those in serum. Smoking may increase production of free radicals, which may pose a particularly increased risk given that studies have also suggested that smokers are relatively deficient in antioxidants. Smoking may also reduce both local and systemic immune functions.

The risk of cervical neoplasia associated with *oral contraceptive use* has been debated. This exposure is difficult to study because sexually active women who are not using oral contraceptives generally use alternative birth control measures, which may also modify risks for HPV infection, persistence, and progression. Although the progesterone content of the pill may induce an ectropion, which could lead to increased HPV exposure or mechanical trauma, this anatomic alteration may also increase the sensitivity of HPV testing and cytology without

affecting the biology of the infection. In the IARC study (111), the use of oral contraceptives for at least 5 years was associated with a three-fold increased risk for cervical neoplasia. Longer duration and recent use were associated with increased risk, whereas risk declined to that of controls after cessation for 6 years. In the IARC study and in a recent review of 19 studies, there was little evidence that the use of the pill was associated with an increased probability of HPV detection (59). These data have been interpreted as suggesting that oral contraceptives act as a promoter of carcinogenesis downstream from the point of HPV persistence. Some studies, however, including a recent analysis of data from a large cohort, have not implicated the pill in cervical carcinogenesis (26).

It has been postulated that birth control pills and pregnancy produce similar hormonal effects with respect to cervical cancer risk. The effect of the pill on cervical cancer risk is important because both family planning and cervical cancer control are critical issues in developing nations.

Based on a synthesis of the epidemiologic literature, Bosch et al. (14) concluded that HPV infection in combination with three cofactors (pregnancy, smoking, and oral contraceptive use) accounts for about 75 percent of cases of cervical cancer, whereas in 25 percent of cases, HPV has been implicated but HPV cofactors have not been identified. Diet, nutrition, unidentified genetic factors, and possibly other sexually transmitted diseases may also affect the natural history of HPV infection. One study has suggested that acute (neutrophilic) inflammation, irrespective of the inciting cause, is an HPV cofactor. This association should be distinguished from chronic (lymphoplasmacytic) inflammation, which may represent a protective immunologic response. If confirmed, this finding might account for inconsistencies regarding the role of specific individual infectious agents as HPV cofactors (25).

Progression of HPV Infection to CIN 3 and Cancer

Although some data suggest risk factor differences between women who test positive for HPV and have normal cytology as compared to those who have a low-grade squamous intraepithelial lesions (113), women with either of these conditions have a strong tendency to clear their infections and revert to negative cytology, especially if young. Data suggest that women who test positive for HPV have a similar risk for progression to CIN 3 irrespective of whether they were diagnosed with histologic CIN 1 or had negative colposcopic examinations or biopsies (31). Data from a natural history study and inferred findings from a cervical screening study suggest that a substantial percentage of CIN 2 lesions regress, whereas CIN 3 lesions tend to persist, at least over 2 years of follow-up (6,122).

A metaanalysis found that HPV types associated with HSIL and carcinomas differ: in HSIL, types 31, 33, 52, and 58 (so called "intermediate risk" types) predominate, whereas in carcinoma, types 16, 18, and 45 are more prevalent (29). Similarly, preliminary findings suggest that cytologic CIN 2 is more strongly associated with intermediate risk types than CIN 3 and carcinoma, perhaps indicating that HPV typing may predict the risk of cancer among women with CIN 2 (190a). This is an area of active investigation.

Epidemiologic risk factors for women with CIN 3 and carcinoma are similar (112). Women diagnosed with CIN 3, however, are generally 10 to 20 years younger than those with carcinoma, suggesting that invasive properties develop slowly. This view is also supported by the observation that microinvasion is usually associated with extensive CIN 3, which presumably has undergone intramucosal expansion over many years (1,106,125,170).

Epidemiology of Cervical Adenocarcinoma

Most epidemiologic studies of invasive cervical adenocarcinoma and its only well-established precursor, adenocarcinoma in situ (AIS), have been limited by the rarity of these tumors. Nonetheless, data indicate that risk factors for cervical adenocarcinoma and squamous carcinoma differ, although both are etiologically related to HPV.

HPV DNA has been detected in over 90 percent of common invasive cervical adenocarcinomas using optimized assays; extremely rare types, such as clear cell, serous, and mesonephric adenocarcinomas may be unrelated to HPV (14,132). In utero exposure to diethylstilbestrol strongly increases the risk for clear cell adenocarcinoma, but the absolute risk remains small,

probably less than 1/1,000 exposed women (61). HPV has also been identified in about 87 percent of cases of AIS, which may represent an underestimate because these data are based on testing that was performed on fixed tissue (101). In contrast to squamous carcinomas, the prevalence of HPV 18 and HPV 16 are comparable in adenocarcinomas (14,132).

Cytologic screening greatly reduces the risk for squamous carcinoma, but historically has provided modest protection against adenocarcinoma. Data from a large population-based registry (1982 to 1992) showed that a history of a reportedly negative Papanicolaou smear afforded only modest protection against the future development of adenocarcinoma and that this protection was entirely eliminated after 2 years (110). Retrospective clinical studies have estimated that a single smear detects only 50 percent of AIS, with only slightly higher sensitivity for invasive adenocarcinoma (146,147). Although sampling errors are the predominant cause of false negative cytology results, screening and interpretation are also contributory. The true sensitivity of cytology may be lower than reported because of undetected cases.

Data from the Surveillance, Epidemiology, and End Results (SEER) program show that women with AIS are 13 years younger than those with invasive adenocarcinoma, suggesting that most adenocarcinomas are preceded by a lengthy preclinical phase, which should permit effective screening (133a). Historically, however, cytologic screening has not been highly effective in preventing adenocarcinoma. Factors that reduce the sensitivity of cytology for detecting AIS include inadequate sampling of lesions located in the endocervical canal or within endocervical invaginations, unfamiliarity with cytologic criteria, and cytologic features that overlap with benign conditions (87,94,146,147). Hildesheim et al. (64) found that young white women with adenocarcinoma and adenosquamous carcinoma were over-represented among patients classified as having rapid onset of disease, defined primarily as a negative Pap smear within 5 years of diagnosis (confirmed on review) and the development of cancer within 10 years of initiation of sexual activity.

Our knowledge of the epidemiology of cervical adenocarcinoma lags behind that of squamous cell carcinoma. Adenocarcinoma seems to share some risk factors with cervical cell squamous carcinoma (acquisition of HPV through sexual contact) and others with endometrial carcinoma (a tumor etiologically related to hormones).

Two risk factors for squamous cell carcinoma, parity and smoking, may not increase the risk for adenocarcinoma (3,17,92,173). In contrast, excessive body weight seems to increase the risk for cervical adenocarcinoma but not for squamous cell carcinoma (17,93,128,173). Oral contraceptives have been linked to an increased risk for AIS or adenocarcinoma in several studies (17,90,101,169,172,173). In some studies, the association between the pill and cervical adenocarcinoma was stronger for long-term users (101,169,172) and in one study, young age, recent or current use, and high progesterone content were also related to risk.

The increased risk of cervical adenocarcinoma associated with obesity resembles the epidemiology of endometrial adenocarcinoma. The relationship between cervical adenocarcinoma and oral contraceptives, however, resembles reported results for squamous cell carcinoma of the cervix. The association between estrogen replacement therapy and increased risk for cervical adenocarcinoma has been inconsistent (91,129) and the use of depot-medroxyprogesterone did not increase the risk in one report (168).

HPV IMMUNOLOGY

Basic knowledge of HPV immunology is essential for recognizing the characteristics of immunodeficient women at increased risk for persistent HPV infection and cervical neoplasia and for understanding the rationale underlying HPV vaccine development. Readers are referred to recent reviews for a more detailed summary of this rapidly evolving subject (86,102,126, 159,160,171,186,191).

Evasion of Host Immune System

The evolution of extreme genotypic diversity has contributed to the success of HPV as a human pathogen. Infection with one HPV type does not preclude concurrent or future infection with other types. In fact, it is unclear whether successful clearance of a specific HPV type prevents subsequent reinfection with the same type.

HPV evades the host immune system through multiple mechanisms. HPV does not lyse keratinocytes; virions are shed within exfoliated keratinocytes, minimizing exposure of the host to immunogenic HPV antigens. In addition, HPV infection does not produce a viremia, which limits stimulation of systemic host immunity. Although bone marrow dendritic cells seem to be capable of stimulating immune responses to HPV antigens, the main antigen-presenting cell in the cervix, the Langerhans cell, cannot induce such responses without costimulatory factors (48).

Paradoxically, tightly regulated protein production may represent an evolutionary adaptation of the virus that helps it evade immune attack. Factors that limit viral protein synthesis include a scarcity of host tRNA molecules that recognize viral codons for L1 and L2 and downregulation of E6 and E7 by E2 in the absence of viral integration into the host genome (171). Once E6 and E7 are synthesized, they are sequestered within keratinocyte nuclei, where they remain largely hidden from the host's immune system in the absence of cellular disruption. Other immunomodulatory effects of HPV include downregulation of major histocompatibility complex (MHC) class II antigens and inhibition of interferon production.

Host Defenses: Squamous Epithelium

Keratinocytes are a physical barrier to infection and also produce interferons, cytokines, and microbicidal peptides that combat pathogens (160,171,191). Interferons inhibit proliferation and induce apoptosis of virally infected cells. Cytokines recruit and activate immune effector cells, including macrophages, natural killer cells, and lymphocytes. Keratinocytes express MHC class I molecules (although weakly) and adhesion molecules that mediate the interaction of the epithelium with the immune system.

Although the squamous epithelium affords some protection against HPV infection, it has been postulated that the balance of immune factors in the cervix normally favors immunosuppression, which might be adaptive given that sexual reproduction involves exposure to foreign antigens in sperm. Keratinocytes function suboptimally as sentinels of the immune system because their expression of HLA class I and II molecules is weak and they do not synthesize the costimulatory cytokines required for effective antigen presentation to immune effector cells. It has been postulated that HPV-transformed cells may dampen immune responses through several mechanisms: the production of inhibitory cytokines, synthesis of molecules that inactivate stimulatory cytokines, and inhibition of activity or promotion of apoptosis of cytolytic T cells (102).

Host Defenses: Immunologic Responses

Immune responses to HPV (and other pathogens) are divided into two distinctive but interrelated mechanisms: innate immunity and adaptive immunity (75). Innate immunity consists of rapid, nonspecific responses to cellular stresses, whereas adaptive immunity is distinguished by clonal expansion of cells that have undergone specific gene rearrangements, resulting in a pathogen-specific response and immunologic memory. The latter promotes a vigorous response to repeated challenges with the same pathogen.

The development of adaptive immunity requires a complex interaction between CD4 T-helper cells, CD8 T-killer cells, B cells, antibodies, and cytokines. In adaptive immunity, foreign antigens recognized by immature dendritic cells are internalized by endocytosis or macropinocytosis and processed into peptides that are complexed with HLA molecules for presentation to T cells in lymphoid tissue. Antigen presentation in the context of HLA class I molecules stimulates CD8-positive cytotoxic T cells, whereas coupling to HLA class II molecules stimulates CD4-positive helper T cells. CD8-positive cells kill virally infected cells and CD4-positive cells produce proinflammatory cytokines.

T-helper cells develop along two pathways with different implications for subsequent events. Type 1 cells produce interleukin (IL)-2, IL-12, and interferon (IFN) gamma, leading to the generation of cytotoxic T cells and natural killer cells. Type 2 cells secrete IL-4, IL-5, IL-6, IL-10, and IL-13, favoring B-cell development and humoral responses. Without the production of appropriate costimulatory molecules, antigen presentation by dendritic cells does not result in an immune response and may result in nonresponsiveness (tolerance).

Type 1 cytokines seem to be associated with a more effective response to HPV infection and

HPV-induced lesions than type 2 cytokines. Data suggest that peripheral blood mononuclear cells obtained from women with extensive HPV disease (CIN 3 associated with additional lower genital tract disease) produced less IL-2 and more IL-4 and IL-10 under experimental conditions than cells obtained from women with CIN 3 only or healthy controls (28a). Al-Saleh et al. (2) found that IL-2–expressing cells were reduced in HSIL compared to normal tissue, whereas the density of IL-4– and IL-6–staining cells was increased in squamous intraepithelial lesions (CIN) compared to adjacent normal tissue. HLA-DR–expressing cells were found only in CIN lesions; expression was higher in more severe lesions. Similarly, Giannini et al. (55) demonstrated that Langerhans cells derived from SILs or the transformation zone produced less IL-2 and more IL-10 than those derived from the exocervix when stimulated in vitro. Another study (115) also found that compared to normal tissue, CIN was associated with: 1) increased expression of HLA-DR, adhesion molecules (CD54/ICMA-1), and immune costimulatory molecules (CD58/LFA-3); 2) failed expression of adhesion and costimulatory molecules in Langerhans cells; 3) reduced expression of TNFα (activator of Langerhans cells); and 4) increased expression of IL-10. Generally, studies have demonstrated that type 2 immune responses are associated with CIN.

Clinical evidence also indicates that cellular immune function is essential for spontaneous elimination of HPV infection. Patients with impaired cellular immunity attributable to HIV infection, transplantation, or use of immunosuppressive drugs have increased HPV persistence, genital warts, CIN, and cervical cancer (9,126,130,164). Histopathologically, regressing warts show dense lymphocytic infiltrates consistent with a cell-mediated response. Evidence that effective cell-mediated immune responses are linked to the outcome of HPV infection has also been demonstrated using systemic measures of immunity. Hopfl et al. (70) found that regression of CIN was associated with delayed type hypersensitivity reactions to cutaneous testing with HPV 16 E7.

Women with deficiencies of humoral immunity do not seem be at increased risk for cervical neoplasia. Serum antibodies against HPV can be found among both women who test HPV DNA negative and those who test positive. Similarly, activation of cell-mediated immunity does not necessarily predict HPV DNA status or disease outcome. The relationship between humoral and cell-mediated immune responses and clinical outcome is the subject of active research. Future studies employing novel techniques promise to provide additional insights into the immunobiology of HPV infection. Available data clearly suggest that humoral responses are important for preventing infection, whereas cellular responses are integral to clearing infection. This dichotomy has driven efforts to develop prophylactic and treatment vaccine strategies.

Human Leukocyte Antigens

HLA antigens seem to play an important role in the development of host immune responses to HPV. Studies have identified specific inherited HLA allelotypes that are related to the risk of cervical neoplasia (178,179). In addition, HPV infection itself is associated with dysregulation of expression of HLA molecules on cells.

Brady et al. (16) demonstrated five mechanisms of HLA downregulation in eight newly developed cervical cancer lines: transcription without protein production for HLA class I; abnormal HLA class I transcription; loss of transcription of HLA-B molecules; loss of HLA expression related to loss of heterozygosity at loci coding for HLA molecules; and loss of responsiveness to IFNγ. An analysis of 17 key immunologic markers found that only 1 of 16 cervical cancers normally expressed all molecules (136). In a prospective study of 88 HPV 16-positive women with untreated SIL, HLA-B44 was expressed among 6 (75 percent) of 8 women with disease progression (defined as colposcopic evidence of greater than two quadrant disease or cytology of carcinoma) as opposed to 20 (25 percent) of 80 without progression. Immunohistochemistry demonstrated loss of HLA-B44 expression in lesions removed from 4 of 5 women whose lesions progressed, whereas loss of HLA class I molecules was not found in 9 lesions that did not progress (12). Downregulation of HLA-B7 is also associated with worse survival in cancer patients. HPV 16 variants that produce mutant E6 with altered binding motifs may lead to weak immune activation in women with HLA-A2 and -B7.

Subversion of Host Immunity

HPVs produce factors that interfere with immune responses to the virus (86,102,126,159, 160,171,186,191). HPV E7 protein blocks the induction of IFNα genes and inhibits the IFNβ promoter. In vitro, exposure to E7 in the absence of inflammation may induce tolerance. The structural similarity of HPV E7 to several human proteins may also reduce its immunogenicity. In cell lines, secreted E6 and E7 may reduce IFNα production in natural killer cells. E6 may also downregulate expression of IL-18, a molecule that launches cytolytic T-cell responses. Acidification of endosomes by HPV E5 may diminish antigen processing and presentation.

Table 3-3

FACTORS INFLUENCING THE OUTCOMES OF HUMAN PAPILLOMAVIRUS (HPV) INFECTIONS

HPV Type (Variants)
HPV Load
Host Genetics
Host Immune Response
Specific Exposures
Parity
Smoking
Oral contraceptive use
Tissue Microenvironment
Properties of infected cells
Interaction of infected cells with other cellular/non-cellular components

CLINICAL APPLICATIONS OF HPV TESTING

The field of HPV testing is rapidly evolving at the time of this writing. Laboratory researchers are actively developing new assays and testing the suitability of various specimen collection media. Translational research is focused on defining clinical applications that will improve patient care and reduce costs (Table 3-3).

Rationale for Clinical HPV Testing

Detection of approximately 15 oncogenic HPV types identifies essentially all women who are at risk for cervical cancer; however, most oncogenic HPV infections, particularly in young women (less than age 30 years), spontaneously regress. Therefore, a negative HPV test provides strong reassurance that cervical cancer or its precursors are not present. Furthermore, the development of cervical cancer generally takes considerably more than a decade of persistent HPV infection, indicating that women who test negative for HPV are not at risk for cancer in the immediate future. Accordingly, an optimal HPV assay must achieve high analytical sensitivity, with high throughput capacity, reasonable cost, reproducibility, technical ease of performance, and compatibility with clinical samples of varying composition.

Clinical HPV Assays

Early attempts to use HPV testing clinically achieved mixed results, in large part because assays lacked both the capacity to detect the broad spectrum of viral types found in cervical neoplasia and the analytical sensitivity to detect low viral copy numbers. Newer methods have addressed these limitations, which has shifted attention to the specificity and cost-effectiveness of testing. Numerous techniques for detecting HPV infections have been developed as of this writing and many others are under development (72). Critical issues in assessing the performance and utility of an assay include the potential application for which the test would be used; the nature of the test sample; the sensitivity, reproducibility, cost, and throughput capacity; and the expertise and equipment required to perform the test. Most clinical testing is performed to identify the presence of oncogenic types in cervical scrapes; testing for low-risk HPV types is not generally indicated in cancer screening. In situ hybridization to detect low-risk types has been used in some laboratories to aid in the histologic diagnosis of condyloma acuminatum.

Most HPV testing is performed on cytologic specimens, which consist of a heterogeneous population of cells that often under-represent the most severe pathology in a patient's cervix. Samples obtained from HPV-infected women may contain numerous uninfected squamous cells, inflammatory cells, and other elements. Even when CIN 3 is present, morphologically normal squamous cells and koilocytes usually predominate. Given that cervical scrapes are inherently limited, it is desirable to perform HPV testing on the same collection used for cytology to ensure that the composition of the cellular sample is known (50,150). Also, the collection of one sample for cytology and HPV testing eliminates the need to perform two scrapes or re-call selected women to

obtain a sample for virologic testing following cytologic interpretation (i.e., ASC-US)

HPV tests are extremely sensitive, and meticulous handling is required to avoid contamination of HPV-negative specimens with HPV DNA derived from positive samples. Cellular samples obtained from women with histologically confirmed CIN usually contain picogram quantities of HPV DNA; detection of lower concentrations of HPV DNA generally contributes little to the detection of CIN or carcinoma. Polymerase chain reaction methods (MY09/11, PGMY09/11, GP5+/6+, GP5/6) are capable of amplifying 40 or more different HPV types, including all types known to cause cervical cancer. Amplicons are typed using a variety of methods, such as gels, dot blots, and line strip hybridization, a method favored in many laboratories. In general, agreement between validated assays has been excellent, especially among women with histologically proven disease.

Although it is impossible to predict which HPV testing methods will be used in the future, a few generalizations about the features of an optimal HPV test are recognized. Specific HPV typing (as opposed to simply reporting that an unidentified oncogenic type[s] is present) has theoretical value in several possible applications. Given that the single-test prevalence of HPV among young women is high and that new infections are extremely common, identification of type-specific persistence (repeated detection of the same type) may be important for assessing risk and determining management. In the post-treatment setting, HPV typing may permit the distinction between persistent infection related to inadequately treated CIN and the development of an HPV infection of a new type. In addition, the efficacy of HPV vaccines requires testing for the HPV types against which the vaccine was directed.

Many studies have assessed whether the HPV load correlates with the severity of prevalent CIN. Among women with ASC-US cytology, HPV load assessment does not seem useful for identifying women who have an underlying CIN 2 or CIN 3 lesion (149,154). The reason is that these women often have small CIN 3 lesions that are associated with extensive CIN 1. Cytologic specimens from these women typically contain a heterogeneous mixture of cells, in which normal squamous cells and low-grade squamous intraepithelial lesion (LSIL) cells (which are relatively rich in HPV DNA compared to HSIL [33,145]) predominate. Therefore, the range of viral load values in women with prevalent CIN 3 is wide and probably more reflective of the CIN 1 lesions with which they are associated. Interpretation of load is further complicated by the use of tests that cannot distinguish between different HPV types in cases of multiple infections. Adjusting HPV load for total genomic DNA has not eliminated the problem of highly variable overlapping values across grades of CIN (165), although some improvement in the detection of CIN 3 has been found specifically for HPV 16-related disease (37).

Some studies that have assessed whether HPV load predicts future risk of disease in cytologically normal women have found that high values for HPV 16 are associated with increased risk for the future development of CIN 3 (76,189). If firmly established, this would suggest that determining HPV 16 load might be useful in primary screening (as opposed to management of ASC-US). The value of assessing serial measurements of viral load in women followed without treatment is also under study.

Expanded clinical access to HPV testing and a growing list of evidence-based indicatons for its use created a need for practice guidelines. These were published in 2009 (http:www.asccp.org/consensus/cytological.shtml) (156a).

The ASCUS/LSIL Triage Study (ALTS)

The ASCUS/LSIL Triage Study (ALTS) was a large multiinstitutional screening trial of over 5,000 women launched by the National Cancer Institute to address problems related to the clinical management of women with ASC (formerly ASCUS) or LSIL cytology (140). After implementation of the Bethesda System in the United States, it became apparent that several million women were receiving cytologic reports of ASC or LSIL each year (39). Although the risk of a single woman with ASC or LSIL having CIN 2 or CIN 3 is low, the huge size of this group led to the paradoxical realization that many and perhaps most women with an underlying CIN 2 or CIN 3 lesion present with ASC or LSIL cytology (79). This posed an important management issue, compounded by the demonstration that the interpretation of ASC is not reproducible

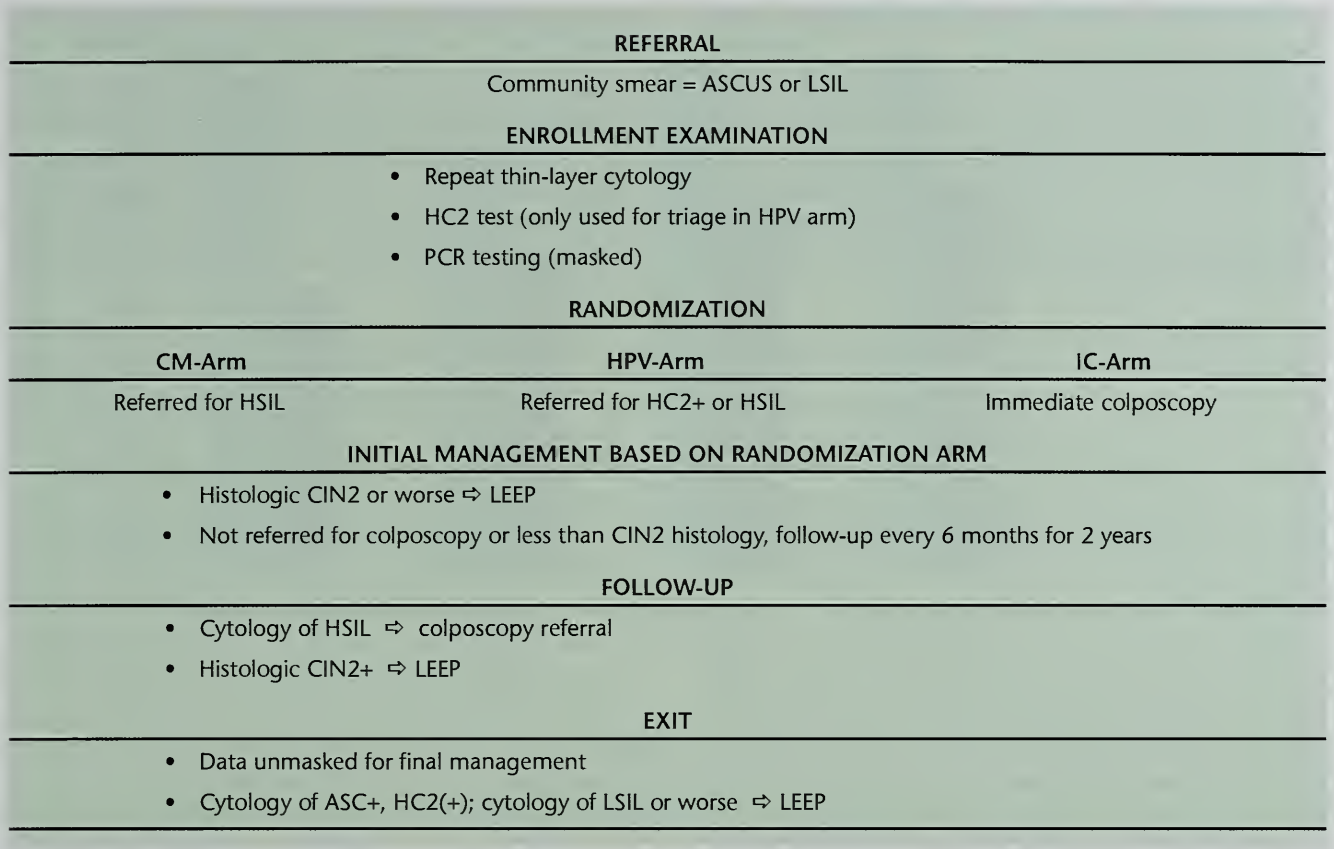

Figure 3-3

OVERALL DESIGN OF THE ASCUS/LSIL TRIAGE STUDY (ALTS)

Note that after enrollment, the follow-up protocol was identical for all subjects. Performance of LEEP for women with persistent HPV infections led to the detection of occult CIN2 and CIN3 lesions that were not detected by cytology or colposcopy. (ASCUS = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion; CIN = cervical intraepithelial neoplasia; HC2 = hybrid capture 2 HPV test; PCR = polymerase chain reaction; HSIL = high-grade squamous intraepithelial lesion; LEEP = loop electrosurgical excision procedure. Note: since completion of ALTS, the term "ASCUS" has been replaced with "ASC," atypical squamous cells. ASC is subdivided into ASC-US (undetermined significance) and ASC-H (cannot exclude HSIL).

among pathologists (151) and that definitive reclassification of ASC as negative or SIL leads to frequent misclassification (133). An additional concern was that the creation of the category of LSIL in the Bethesda System would increase colposcopy referrals because koilocytotic atypia and CIN 1 were now considered comparable findings with respect to management.

The ALTS compared three approaches for managing women with community smear interpretations of ASC or LSIL: conservative management with repeat thin-layer cytology (CM-Arm), HPV DNA testing for oncogenic types (HPV-Arm), and immediate colposcopy (IC-Arm) (fig. 3-3) (140). The threshold for referral in the CM-Arm was liquid-based cytology of HSIL. In the HPV-Arm, women were referred for either a positive test for oncogenic HPV DNA or repeat cytology of HSIL, although the latter was inconsequential with regard to added sensitivity. The main outcomes in ALTS were detection of histologic CIN 3 (immediate precursor of carcinoma); detection of CIN 2 or worse (common treatment threshold in the United States); and the number of women referred for colposcopy. Women were enrolled at four clinical centers approximately 8 weeks following the initial smear of ASC or LSIL. At enrollment, subjects underwent a pelvic examination, collection of a liquid-based cytology specimen, and cervicography followed by randomization to one of the three trial arms.

The repeat cytology sample was used to prepare a thin-layer slide and to perform HPV DNA testing for 13 oncogenic viruses at a threshold

of 1.0 pg/mL (about 5,000 viral copies). HPV testing was also performed on a second cellular sample retrospectively using a polymerase chain reaction-based method, but this was not used for management. Although HPV testing was performed on all subjects, results were masked in the CM-Arm and IC-Arm. Following randomization, women were either referred for colposcopy or asked to return in 6 months.

Women who were referred for colposcopy and received a histologic diagnosis of CIN 2 or a more severe interpretation were treated with loop electrosurgical excision procedure (LEEP). To ensure subject safety, a small number of women were referred for colposcopy based on quality control review of the smears, liquid-based cytology preparations, histologic specimens, or cervigrams.

After enrollment, all women were followed every 6 months for 2 years with repeat thin-layer cytology and colposcopy referral for HSIL. Therefore, the management protocol for subjects in ALTS differed by the randomization arm at enrollment only. After 2 years of follow-up, women participated in an exit visit which included colposcopy for all subjects and LEEP for any woman with persistent LSIL, persistent ASC associated with oncogenic HPV infection, or HSIL and above. The exit visit detected cases of CIN 2 and CIN 3 that were not identified cytologically or colposcopically. Most follow-up cytology and all histologic specimens obtained in follow-up were also reviewed by the pathology quality control panel to provide added safety and to develop a set of consensus interpretations. A small percentage of patients were referred for colposcopy based on safety net determinations made by colposcopy or pathology quality control groups.

Key Enrollment Findings in ALTS: ASC Triage. At enrollment, a comparable number of women with histologic CIN 2 or above were identified by HPV testing or immediate colposcopy (157). In contrast, a colposcopy referral based on repeat thin-layer cytology of HSIL detected about 50 percent fewer lesions. Further enrollment analyses based on data generated in the two sensitive arms (HPV-Arm and IC-Arm) demonstrated that repeat cytology, even at the maximally sensitive threshold for colposcopy referral of ASC or worse, would have detected only 85 percent of CIN 2 or CIN 3 lesions. HPV testing demonstrated 96 percent sensitivity for CIN 2 or CIN 3 while referring an approximately equal number of women as would have been referred at a threshold of ASC for repeat cytology. A single repeat cytologic test is inadequate to exclude CIN 2 or CIN 3 in women with ASC, suggesting that at least two negative results following an interpretation of ASC may be required before resumption of routine screening.

It has been noted that repeated cytologic testing may add cost, delay diagnosis, increase loss to follow-up, heighten patient anxiety, and ultimately lead to a high percentage of colposcopy referrals in aggregate when cytologic examinations are repeated two or three times. Cox estimated that to reduce nondetection of high-grade CIN to approximately 2 percent among women with an initial ASC would require three repeated conventional Pap smears or two repeated thin-layer cytology tests, and that two repeated conventional Pap smears would refer over 70 percent of women to colposcopy. Immediate colposcopy for all patients with ASC would place a strain on qualified colposcopists and seems unwarranted for usual patient populations in which the risk of carcinoma is only about 1/1,000 (30). A clinical consensus was reached that HPV testing for oncogenic types is the "preferred" method for managing ASC-US when testing is performed using a specimen collected concurrently with the initial ASC-US cytologic specimen. Repeat cytology is "acceptable" management (187).

The specificity of both repeat cytology and HPV testing was higher among older women, but improvement, compared to results for younger women, was much greater with HPV testing (fig. 3-4). In ALTS, among women aged 29 years and older, HPV testing identified 94 percent of CIN 3 lesions and referred only 31 percent of patients whereas repeat cytology detected 91 percent of women with histologic CIN 3 and referred 50 percent of women for colposcopy. Referrals using HPV testing declined further among women aged 39 years and older. The age-specific results of cytology and HPV testing in detecting CIN 2 or worse were similar to those for CIN 3 (149). These data underscore the significant improvement in the performance of HPV testing for colposcopy triage of older women with ASC-US, which reflects the lower prevalence of transient infections among older

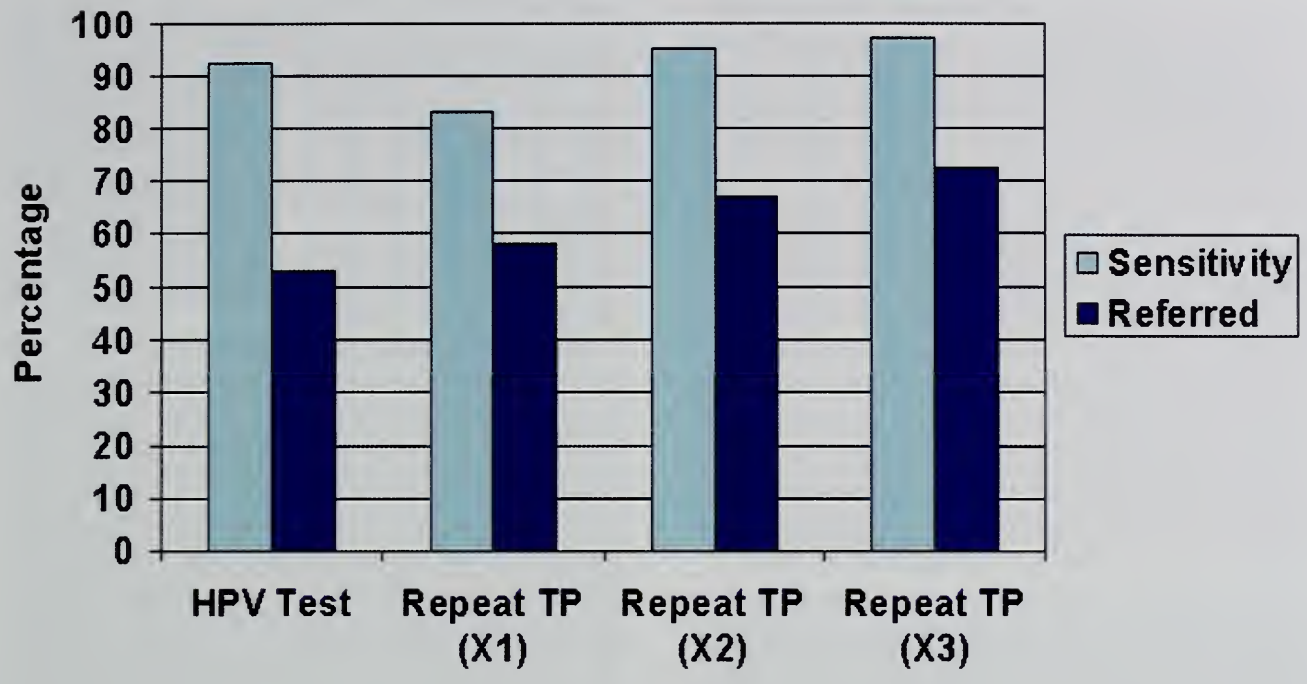

Figure 3-4

DETECTION OF CIN 3 AMONG WOMEN REFERRED WITH ASC IN ALTS: COMPARISON OF A SINGLE HPV TEST WITH CUMULATIVE RESULTS OF REPEAT THINPREP (TP) CYTOLOGY

For women enrolled in ALTS with ASC, the percentage with histologic CIN 3 or worse detected at any time during trial among women referred to colposcopy (sensitivity) and the percentage of women in each arm (regardless of underlying pathology) referred by triage test (left to right): single test for oncogenic DPV DNA at enrollment and repeat thin-layer cytology of ASC or worse, based on one, two, or three repeat examinations.

women. These data also highlight the value of HPV testing in women with ASC-US: negative results provide strong reassurance to approximately 50 percent of women.

Key Enrollment Findings in ALTS: Colposcopy Triage of LSIL. Historically, data suggested that a cytologic interpretation of LSIL was suspect, particularly in older women, because many such subjects did not test positive for HPV DNA and the cytologic interpretations of LSIL could not be independently confirmed (141). Concerns that overinterpretation of LSIL would result in unnecessary follow-up and treatment were magnified by the growing recognition that most of these lesions spontaneously regress in young women. ALTS was designed to address the historical problem of overinterpretation of LSIL by evaluating the same three management protocols that were examined for determining the need for colposcopy referral of women with ASC.

A preliminary analysis of enrollment data demonstrated that 83 percent of women with cytology of LSIL reported in community laboratories tested positive for oncogenic HPV types and that 80 percent had repeat cytologic interpretations of ASC or worse (71). Raising the threshold for referral to repeat cytology of LSIL was unacceptably insensitive for identifying women with an underlying CIN 3 lesion. These data led to the interpretation that neither repeat cytology nor HPV testing could produce a meaningful reduction in colposcopy referrals without reducing the detection of women with CIN 3. Notably, HPV 16, the prototypic oncogenic HPV, was detected in 25 percent of women with LSIL, disproving the notion that low-risk HPV types account for most LSIL cytology.

The HPV-Arm of the ALTS for women referred with LSIL was closed prematurely when it was determined that the high percentage of women who tested positive precluded clinical utility. Detection of HPV among women with LSIL was not dramatically different for older women, but the ALTS enrolled relatively few older patients. Some researchers maintain that HPV testing may still have some value in managing older

women with LSIL. Subsequently, it was determined that the CM-Arm was insensitive in detecting women with LSIL cytology who had an underlying CIN 3 and subjects in this arm were referred for immediate colposcopy.

Other Key Enrollment Findings in ALTS. The vast majority of CIN 3 lesions associated with ASC that were detected in ALTS were small, suggesting that delayed detection for months or years would most likely still have permitted treatment prior to the development of invasion (154). However, findings in ALTS also suggested that CIN 3 lesions do not regress to lower-grade lesions during 2 years of follow-up (5,6). Given the unpredictable behavior of individual CIN 3 lesions, sensitive detection and treatment of all CIN 3 lesions remain the standard of care.

The pathology quality control panel review of the smears and liquid-based preparations collected at enrollment divided interpretations of ASC into those that were suggestive of HSIL (ASC-H) and those that were suggestive of grades of SIL of less severity (ASC-US). An analysis of these data showed that interpretations of ASC-H on both smears and liquid-based slides was associated with a higher percentage of HPV detection and a considerably higher percentage of underlying histologic CIN 2 and CIN 3 (153). However, the percentage of women with ASC-H cytology who had underlying CIN 2 or worse was considerably less than that associated with HSIL cytology. The interpretation of ASC-H was relatively rare compared with ASC-US. Cytologic criteria for these entities are described and illustrated elsewhere in this and other volumes. Based on these data, it was determined that colposcopy referral is the "preferred" management for women with ASC-H. If colposcopy and biopsy do not demonstrate CIN 2 or worse, all data should be reviewed to determine the need for additional follow-up or treatment (187).

The ALTS provided a unique opportunity to rigorously compare the interobserver reproducibility of cytologic interpretations and histologic diagnoses. A surprising finding was that the overall reproducibility of cytologic interpretations and histologic diagnoses of smears and LEEPs was similar, although areas of disagreement varied (162). The least reproducible cytologic category was ASC, whereas the most problematic histopathologic diagnosis was CIN 1.

One limitation of the ALTS is that multiple technologies have emerged since the trial ended. These methods include computer-assisted screening, application of molecular markers to cytology, new HPV testing methods, and combined approaches. Next generation studies are needed to evaluate these approaches, particularly in anticipation of the future impact of HPV vaccines (see below). This topic is beyond the scope of this chapter.

Follow-up Data from ALTS. At the exit visit in ALTS, women with persistent HPV infections were treated with LEEP irrespective of cytology results or colposcopic impressions, thereby ensuring that all CIN 2 or CIN 3 lesions were identified. Given that women were randomly assigned to each treatment arm, it might be anticipated that the total percentage of women in each arm that reached the trial endpoints of CIN 2 and CIN 3 would be equal; however, this was not the case. Although the detection of CIN 3 was similar in each arm, approximately 40 percent fewer CIN 2 lesions were found among women randomized to the CM-Arm as compared to those managed with immediate colposcopy (5,6). These data suggest that spontaneous regression of CIN 2 occurred frequently among women in whom detection and treatment of CIN 2 was delayed, consistent with previous reports (122). This underscores the need to develop methods for identifying which lesions classified as HSIL require treatment. Based on these data, a management consensus conference suggested that careful follow-up of CIN 2 lesions without destructive treatment may be acceptable management for young women (187).

Follow-up data compared the sensitivity of each management strategy and the number of women that would have been referred for colposcopy. Sensitivity was analyzed in two ways: 1) the percentage of all CIN 3 (or CIN 2) lesions detected at enrollment as compared to the entire 2-year period (for the CM-Arm detection at enrollment or during follow-up was compared to the total because cytology is presumed to achieve cumulative sensitivity through repeat testing) and 2) the percentage of women who were diagnosed with CIN 3 at any time in the trial who were referred to colposcopy by the particular management strategy of the arm. This calculation credits a management technique with detecting disease

if it referred the patient to colposcopy at enrollment even if that examination and the resulting biopsies did not identify CIN 2 or CIN 3.

Follow-up Data from ALTS: Women Referred for ASC. Among women referred to the trial with smears reported as ASC, the cumulative detection of CIN 3 over the 2-year period of the trial was between 8 and 9 percent in the three arms (6). Among women referred to the trial with ASC, data on the percentage referred to colposcopy and the detection of cumulative CIN 3 at enrollment were: CM-Arm, 12 percent and 55 percent; HPV-Arm, 56 percent and 72 percent; IC-Arm, 100 percent and 54 percent. It is notable that masking colposcopists to arm status may have been flawed: women with a positive HPV test or cytology of HSIL were referred in a delayed fashion and may have received closer scrutiny than those referred to immediate colposcopy on the day of enrollment. Among women in the HPV-Arm, 92 percent of subjects who were diagnosed with CIN 3 at any time during ALTS were referred to colposcopy for a positive HPV test. To achieve comparable sensitivity with repeat cytologic testing would have required referral for ASC on either of two repeat examinations, which would have referred 67 percent of women for colposcopy (fig. 3-4).

Follow-up Data from ALTS: Women Referred for LSIL. The cumulative detection of CIN 3 was approximately 15 percent in the three management arms (5). Results for the HPV-Arm were limited by early closure. The IC-Arm detected 56 percent of CIN 3 cases at enrollment, whereas the CM-Arm protocol (colposcopy referral for repeat cytology of HSIL) detected 48 percent of CIN 3 lesions and referred 19 percent of subjects for colposcopy. Lower cytologic thresholds for colposcopy referral would have increased sensitivity, but this would have led to an unacceptably high percentage of referrals. The conclusion was that colposcopy referral is currently the only available management for patients with LSIL cytology.

Data from ALTS: Management Following Colposcopy. The cumulative risk of CIN 2 or worse among women with cytologic LSIL and those with ASC associated with the detection of oncogenic HPV was essentially identical (28 and 27 percent, respectively). Among women who were not diagnosed with CIN 2 or worse as a result of an initial colposcopy, the subsequent risk of CIN 2 or worse in follow-up was similar irrespective of the findings (31). Detection of CIN 2 or worse among women following negative colposcopy and after colposcopy associated with a negative biopsy was 11 percent; CIN 2 or worse was detected among 13 percent of women with histologic CIN 1. These data prompted two conclusions: 1) a single colposcopy, with or without biopsy, does not identify all women subsequently diagnosed with CIN 2 or worse and 2) the risk among HPV-infected women with entirely negative findings and those with histologic CIN 1 is similar. Accordingly, a single postcolposcopy management strategy would be appropriate for these women.

Table 3-4

POSSIBLE CLINICAL APPLICATIONS OF HUMAN PAPILLOMAVIRUS (HPV) DNA TESTING

Colposcopy triage of ASC-US[a]
Colposcopy triage of AGC
Colposcopy triage of LSIL in older women
Quality control of cytopathologic interpretations
Surveillance following treatment of CIN or carcinoma
Primary screening
Evaluating eligibility for supracervical hysterectomy
Confirming a cervical origin for a metastatic lesion

[a]ASC-US = atypical squamous cells of undetermined significance; AGC = atypical glandular cells ; LSIL = low-grade squamous intraepithelial lesion; CIN = cervical intraepithelial neoplasia.

Follow-up data from ALTS indicated that a repeat HPV test performed 12 months following colposcopy without treatment would detect 92 percent of CIN 2 or more severe lesions while referring 55 percent for repeat colposcopy (60). Repeat liquid-based cytology performed at 6 and 12 months with repeat referral for any interpretation of ASC or worse would detect 88 percent of CIN 2 or worse and refer 64 percent for colposcopy. HPV load, colposcopic impression, and combining cytology with HPV testing in follow-up would not improve management. Therefore, semiannual repeat cytology or HPV testing at 1 year were determined to represent preferred management for women who undergo colposcopy without receiving a diagnosis of CIN 2 or worse.

HPV Testing for Management of Atypical Glandular Cells

Data related to the performance of HPV testing for managing women with atypical glandular

cells (AGC) is sparse at this time (Table 3-4). In a study of 137 patients, HPV testing identified 94 percent of women with underlying histologic adenocarcinoma in situ (AIS) or CIN 2 or worse, while referring 29 percent of patients, whereas repeat conventional cytology detected 63 percent of these lesions and would have referred 33 percent of women to colposcopy based on a threshold of ASC or AGC (137). Another study of 106 patients with AGC found that HPV testing was 83 percent sensitive in detecting clinically significant disease, with a positive predictive value better than that generally achieved for ASC-US (87). Similarly, a recent retrospective analysis found that HPV testing for cytology of atypical endocervical cells resulted in both a sensitivity and specificity of 91 percent (27a). Although the available data are promising, HPV testing for managing AGC remains investigational at the time of this writing. Women with AGC who test positive for HPV DNA present a complex differential diagnosis that includes AIS alone, AIS with CIN, CIN alone, HPV infection without pathologic evidence of CIN or AIS, and an endometrial lesion that accounts for the AGC and an unrelated HPV infection. Therefore, even if HPV testing for managing AGC is adopted in the future, careful integration of cytologic, histologic, and colposcopic findings will always be required for the management of these women.

HPV Testing for Quality Assurance of Cytologic Interpretations

Although numerous approaches for monitoring the quality of cytologic interpretations have been proposed, many programs employ several strategies. Microscopic review of cytologic slides and comparison with histology are the mainstays of cytology quality assurance, but this approach is limited by the subjectivity of microscopic interpretation, sampling errors, biases in unmasked reviews, inaccessibility of patients' slides, and lack of adequate follow-up. Comparison of HPV data to cytologic interpretations represents another useful quality assurance measure, especially in laboratories that routinely perform HPV testing for colposcopy triage of ASC-US (151,190).

Studies have demonstrated that detection of oncogenic HPV types is strongly associated with the severity of expert cytologic interpretations, whereas detection of low-risk types is unrelated. Using any accurate HPV test for oncogenic types, the frequency of detection among women with negative cytologic interpretations should be relatively low compared to women with slides classified as SIL. Although results may vary among populations and with use of different testing methods, detection of oncogenic HPV is usually less than 20 percent among women with negative cytology and above 70 percent for women with SIL. The percentage of women with ASC-US who test positive for oncogenic HPV DNA should be intermediate between that of women with negative cytology and those with SIL. HPV detection among women with ASC-US is between 40 and 60 percent in most general screening situations, although a higher percentage may be found in settings with a high proportion of young patients (less than 30 years of age).

If specimen collection and HPV testing are carefully preformed, a high percentage of HPV detection among women with negative cytology suggests that cytologic screening is insensitive. In contrast, failure to detect HPV in a high percentage of women with SIL suggests an excessive number of cytologic false positive results. Similarly, the frequency with which the ASC-US category is used and the percentage of ASC-US interpretations associated with HPV detection provides information regarding the use of this category. Frequent reporting of ASC-US associated with a low percentage of HPV detection suggests excessive use of this category. Comparison of HPV test results with cytologic interpretations facilitates quality assurance assessment of individual cytologists, entire laboratories, and temporal trends. Data from the ALTS suggest that the frequency of HPV detection among women with ASC-US is similar for smears and thin-layer slides (153).

HPV Testing for Primary Screening

Although cytologic screening is specific, the sensitivity of a single test is low. Until recently, annual testing was recommended based on the concept that progression of precursor lesions to invasive carcinoma requires many years, which allows the cumulative sensitivity of repeated testing to achieve better results than would be possible with less frequent screens. The sensitivity of cytology ostensibly improved in the

1990s, but this was associated with increased reporting of ASC-US throughout the decade and aggressive management for all women receiving this report. The result has been that improved sensitivity has come at the cost of huge expense, inconvenience, and psychological discomfort for many women in whom subtle inflammatory changes have been reported as ASC-US in an effort to ensure that a lesion has not been missed. This has prompted efforts to develop more effective screening approaches.

Multiple studies have compared the performance of HPV testing to cytology for primary screening in detecting prevalent disease (20,52,108,123). Based on a summary of 13 studies, Franco (52) concluded that cytology performs with a sensitivity of 60 percent and a specificity of 95 percent for detecting CIN 2 or worse, whereas HPV testing achieves about 85 percent sensitivity and 84 percent specificity. In studies that have restricted enrollment to women aged 30 years and older, HPV testing had a sensitivity of 89 percent and an improved specificity of 90 percent. Data from clinical trials designed to assess the performance of primary screening using HPV testing are ongoing. Initial data from the HPV in Addition to Routine Testing (HART) study (36) of over 11,000 women aged 30 to 60 years found that HPV testing achieved a sensitivity of 97 percent and a specificity of 93 percent for detecting histopathologic CIN 2 or worse. The sensitivity of HPV testing exceeded that of cytology (ASC or worse) but was less specific. The authors concluded that for women over age 30 years, primary screening using HPV testing in combination with cytology to triage those with positive virologic tests is an option. At the time of this writing, results of three large studies have been published strengthening the conclusion that HPV testing has value in primary screening (20,108,123).

Few studies have assessed the value of HPV testing in predicting the future risk of developing disease over a period of lengthy follow-up. In a cohort of 20,000 women who were tested once at baseline, the cumulative incidence among those with either a smear comparable to ASC-US or worse and/or a positive test for oncogenic HPV DNA was 4.5 percent versus 0.2 percent for those who were negative by both cytology and HPV testing after 45 months (148). Whereas cytology largely predicted prevalent disease, HPV testing indicated risk for both prevalent disease and future diagnosis. The US Food and Drug Administration has approved the use of HPV testing in combination with cytology for women aged 30 years and above provided that women who test negative are deferred from screening for at least 3 years. Although HPV testing adds cost, it is hoped that this can be offset by performing more sensitive combined cytologic and virologic screening at less frequent intervals than would be the norm using cytology alone.

HPV Testing for Post-treatment Follow-up

Following conservative treatment of CIN (without hysterectomy), patients are usually followed at close intervals for up to 2 years to exclude a recurrence. Follow-up may be especially important for women treated by LEEP because the margins often appear to be positive histopathologically, cannot be reliably assessed because of specimen fragmentation or cautery artifact, or have little predictive value for identifying women who later develop recurrent CIN. Furthermore, the sensitivity of post-treatment cytology and colposcopy may be reduced by treatment: repair of denuded surface epithelium with morphologically normal epithelium may mask small foci of CIN within endocervical invaginations. Small foci of residual CIN 3 remaining after treatment are particularly concerning because such lesions may represent incipient carcinoma despite their small size. Methods to reduce the intensity of follow-up for women who have been adequately treated and improve early detection of recurrences would be helpful.

Clinical studies assessing the value of HPV testing in post-treatment follow-up have varied with regard to the grades of CIN studied, treatments employed, and HPV assays used. Although most investigations have been small, with limited duration of follow-up, data suggest that women who have negative post-treatment HPV tests have limited risk for CIN, especially CIN 2 and 3 (10,45,74,85,89,98,121). One prospective observational analysis of 765 women followed after LEEP or cone biopsy performed for CIN 2 or worse disease, found that a single HPV test achieved a negative predictive value of 94 percent, which increased to 97 percent with three tests. Although HPV testing along with abnormal cytology and

margin status was a significant predictor of recurrence, HPV was detected in close to 50 percent of women without documented recurrent CIN 2 or more severe disease. This analysis only assessed the clinical value of testing for any of 13 oncogenic HPV types as a group, rather than testing for the specific type that was associated with the lesion that was treated (27).

The explanation for the effectiveness of destructive treatments is not immediately evident, given that HPV infections may widely affect the low genital tract. One theory offered to explain the effectiveness of CIN treatments is that the distribution of the virus may differ between women with CIN and those with clinically occult infections: among women with CIN, the virus may be concentrated within the CIN lesion, whereas in occult infections, the virus may be more evenly and diffusely distributed. This would suggest that elimination of CIN affects a dramatic reduction in viral load within the cervix (167). In addition, excision or destructive treatments may evoke protective immune responses or render the transformation zone resistant to re-infection. For testing to have long-term negative predictive value, patients who clear HPV immediately post-treatment must not become reinfected from a reservoir outside of the cervix (i.e., vagina or vulva) or from their infected partners. In evaluating post-treatment follow-up, it is important to determine whether CIN lesions detected post-treatment reflect recurrences of inadequately treated lesions related to the same HPV type or lesions related to new post-treatment infections with different HPV types.

Some studies have compared the HPV test results following LEEP to the pathologic findings in a subsequent hysterectomy performed after a short interval. Jain et al. (74) reported that HPV was detected in 79 percent of women with positive LEEP margins as compared to 22 percent with negative margins. None of 10 women with positive margins and a negative HPV test had residual CIN in their uteri. Lin et al. (98) reported that HPV testing achieved 100 percent sensitivity and 48 percent specificity for predicting the presence of residual CIN in a hysterectomy following LEEP.

Although studies suggest that HPV testing has promise for use as a follow-up test for detecting disease post-LEEP, especially among women with pathologically involved margins, larger studies with longer follow-up are needed. If successful, this management strategy would greatly reduce the cost and inconvenience of intensive post-treatment follow-up for women with negative HPV tests. Studies of this type may also provide useful information about the effectiveness of different treatments. If successful treatment is associated with type-specific viral clearance, post-treatment testing may also have utility as a quality assurance strategy for assessing the performance of treating physicians. Studies of women post-treatment may provide additional insights into the interactions between HPV, the host immune system, and the transformation zone, and factors affecting sexual transmission of the virus.

HPV VACCINES

Rationale for Developing HPV Vaccines

The vast majority of cervical cancer deaths occur in the poorest nations of the world, where resources for screening and management of detected disease are limited. A prevention strategy that would reduce the reliance on screening is the most attractive approach to achieving cancer control worldwide. Ideally, a vaccine with both prophylactic and therapeutic effectiveness should be developed, which would reduce cancer risk among millions of unscreened, HPV-infected women quickly and prevent the development of HPV infections in others approaching the age of sexual initiation. In general, however, more progress has been made in developing prophylactic vaccines than treatment vaccines (38,57,76a,99,100,142–144,161).

Prophylactic HPV vaccines must be safe because they are administered to healthy individuals, including girls, and potentially boys. The primary reason to vaccinate boys would be to reduce viral transmission, because HPV-related cancers are rare among men. The development and administration of a multivalent vaccine with activity against HPV 6/11 (agents of condyloma acuminatum) and possibly other sexually transmitted diseases would benefit both men and women. Administration should be achievable in resource-poor countries. Low cost, stability without special storage conditions (i.e., refrigeration), and effectiveness with a single administration would be highly desirable. Protection

against cancer would need to last for years to limit the economic and logistical burden of frequent revaccination. In countries with effective screening programs, more rigorous standards might be required, such as reducing the need for screening and preventing the development of cancer precursors. An additional benefit of prophylactic vaccine is the prevention of cancers at noncervical sites as well. Achieving these aims could reduce costs, morbidity, and patient anxiety.

Prophylactic Vaccines

Historically, the inability to produce abundant HPV virions in vitro dimmed prospects for developing an attenuated virus vaccine. Furthermore, concerns over the risk associated with exposing healthy people to oncogenic HPV DNA made this approach unattractive. The development of peptide vaccines failed because it was impossible to recapitulate the three-dimensional conformations characteristic of immunogenic epitopes. A major breakthrough was achieved when it was discovered that it was possible to produce virus-like particles (VLPs) by overexpressing L1 protein using recombinant DNA techniques. VLPs produced by self-assembly of L1 share the morphologic and immunologic properties of complete virions, but lack unwanted viral DNA. L2 can also assemble into VLPs when coexpressed with L1.

VLPs have been studied extensively in cattle, rabbits, and dogs with consistently promising results (143). The systemic administration of VLPs in animal models is highly protective against viral challenges applied to abraded epithelial surfaces of skin and mucosa; papillomas rarely form in vaccinated animals under conditions that lead to papilloma formation in controls. Passive transfer of serum or immunoglobulin (Ig)G from vaccinated animals to naive animals is similarly protective. Rabbits vaccinated with VLPs successfully mounted protective challenges 1 year later. Vaccination of 60,000 beagles with formalin-treated wart extract led to complete protection against the formation of canine oral papillomas as compared to a historical incidence of 10 percent in the same breeding center. It was noted that protective VLP vaccination was species specific, type specific, and dependent on the preservation of conformational epitopes (denaturation abrogated the protective effect). Vaccination with VLPs has no effect on existing lesions.

Readers are referred to excellent comprehensive reviews that summarize the results of clinical trials assessing the efficacy of prophylactic HPV VLP vaccines (107,139a). The majority of data currently available relates to the efficacy of bi-valent (directed against HPV 16 and 18) and quadrivalent (HPVs 16, 18, 6, and 11) vaccines in preventing persistent infections and type-related CIN 2 or 3 among women ranging in age from late teens to mid-twenties who met specific enrollment criteria. Criteria included having had a limited number of lifetime sexual partners, negative prior screening histories, negative HPV DNA tests and negative serology, and having completed a full three-dose vaccine administration regime. These studies found that efficacy at 4 to 5 years of follow-up for preventing persistent infection and type-related CIN 2 or 3 is extremely high or 100 percent. The effectiveness of vaccines when given to less restricted groups of patients (HPV DNA test positive), however, seems much lower than the efficacy achieved in randomized placebo-controlled trials.

If vaccinated patients are below the age of sexual initiation, they can be assumed to be unexposed to HPV. However, neither a negative HPV DNA test nor a negative serologic assay accurately predicts prior exposures to HPV, and therefore, these tests as currently configured do not seem useful for selecting which sexually active women are likely to benefit from vaccination. Recommendations of major organizations regarding who should be vaccinated do not fully agree. The American Cancer Society recommends vaccination for girls aged 11 to 18 years, while deferring judgement for those aged 19 to 26 years, based on discussions between physicians and patients. The Advisory Committee on Immunization Practices recommends vaccination for girls aged 11 to 26 years. Vaccination is permissible as early as age 9 years and not recommended for women over 26 years or males. Continued screening is recommended for all women. To date, side effects related to vaccination have been limited in severity, but additional data are needed. A recent analysis did not find a significant association between vaccination and miscarriage, but further surveillance is needed (175a). In addition, the duration of protection for vaccinated girls in the

target age range, especially the youngest girls, has not been determined.

Successful vaccination against HPV 16 would have a tremendous impact worldwide because this viral type accounts for approximately 50 percent of cervical cancers. More complete protection would require the development of polyvalent vaccines protective against additional types. Data suggest that a vaccine directed against 4 to 6 HPV types could theoretically prevent up to 80 percent of cervical cancers and would also potentially reduce the incidence of tumors of the vagina, vulva, anus, and possibly nonanogenital sites (14). Recent data from a national vaccination program showed that administration of the quadrivalent vaccine was associated with a decline in the number of patients presenting with genital warts, providing early evidence of vaccine effectiveness in clinical practice (47a). Data suggest that reducing the incidence of one or more HPV types will probably not lead to compensatory increases in the frequency of persistent infection with other types, although this critical topic requires additional study (97,138). Clinical prophylactic vaccine trials based on immunization against L2 have also been initiated (77).

Therapeutic Vaccines

E6 and E7 represent attractive targets for therapeutic vaccines because these proteins are required for maintaining the transformed state. Efforts have focused initially on E7 because it is more abundant than E6 in host cells, possesses a more highly conserved structure, and has been better characterized immunologically.

HPV-related peptides have been identified that bind to specific MHCs and activate T-cell receptors. The development of peptide vaccines is complex because different human leukocyte antigen (HLA) allotypes may be able to present a restricted repertoire of peptides. Although induction of tolerance and mutation of targeted oncogenes in tumors are potential concerns, the former may be avoidable with the correct route of administration and the latter is presumed to occur rarely. An advantage of protein-based vaccines over peptide vaccines is that HLA allele restriction is not an issue because antigen processing takes place in host macrophages and dendritic cells and the immunogenic epitopes are combined with newly synthesized HLA molecules. In peptide-based vaccines, the immunized peptide displaces other peptides already HLA bound. Multiple immunizations and the use of adjuvants might be required with protein-based vaccines because of rapid degradation.

Theoretically, DNA-based vaccines would represent a relatively inexpensive approach suitable to large-scale production that would lead to sustained expression of antigen in the host. Inclusion of multiple genes and autologous antigen processing would represent advantages. Mutant forms of oncogenes would be required to avoid cellular transformation. RNA-based vaccines represent another option that has been considered.

Vaccination using a variety of viral or bacterial vectors has been suggested. Vaccinia and adenovirus in particular have received attention because they can accept large DNA insertions that are actively transcribed, resulting in high levels of antigen exposure in the host. Vaccinia viruses are lytic, which makes integration of foreign DNA into human recipients unlikely. Replication deficient strains of adenovirus and canarypox, a virus that does not replicate in human cells, are possible viral vectors. Attenuated forms of *Escherichia coli, Salmonella, Shigella,* and *Listeria* have also been proposed as vectors. *Listeria* has the unusual property of delivering antigens to both the class I and class II HLA systems because of its ability to exist both within phagosomes and free in the cytoplasm.

Dendritic cells or tumor cells may also be used to prepare vaccines. Dendritic cell vaccines are produced by treating the patient's harvested hematopoietic precursors with cytokines, followed by exposure to immunogenic peptides or proteins or transduction with *E6* or *E7* DNA or viral vectors containing these gene sequences. Injection of modified tumor cells back into patients has been tried as immunotherapy for other tumor types and also has been considered an option for treating advanced cervical cancer.

Trials of chimeric VLPs consisting of E6 or E7 peptides or DNA enclosed and protected with HPV pseudovirions have been planned. It is hypothesized that this mode of antigen delivery may effectively deliver antigens to dendritic cells and lead to an enhanced response because VLPs upregulate HLA molecules. As with some methods that use pathogenic organisms as vectors,

there are theoretical concerns that preexisting antibodies (in this instance against L1) may reduce the effectiveness of this approach.

HPV Vaccine Research

Prevention of type-specific persistence and the development of CIN 2 and 3 are reasonable endpoints for trials of prophylactic vaccines. More direct measures of effectiveness, such as population-based reduction in incident HPV infections and cancer, will be more difficult to ascertain and take long periods of time. The effectiveness of polyvalent vaccines and the optimal route and vehicles for delivery must be determined. Evidence suggesting that L2 epitopes may provide protection against several HPV types suggests another method for achieving broader protection, but L2 is less antigenic than L1, and a method for upregulating immune responses to L2 is an area of inquiry (77).

Measures of the effectiveness of therapeutic vaccines will also need to be defined. To date, most studies of these agents have focused on patients with advanced cancer, but data suggest that treatment of women with earlier (noninvasive) disease may be necessary to uncover the full potential of these vaccines.

Widespread vaccination may have an important impact on screening, a field which is already rapidly changing to incorporate our increased knowledge of cervical carcinogenesis and the development of new technologies (152). Effective vaccination against HPV types with the greatest oncogenic potential (e.g., HPV 16) would both reduce the total prevalence of HPV infection and the virulence of the viruses remaining in populations. This would result in fewer SILs, and the SILs that would be detected would have less potential to progress. Manual screening of slides would become increasingly tedious with limited cost-effectiveness. Consequently, automated screening of cytologic slides, noncytologic methods, or manual screening of populations stratified according to risk (based on HPV DNA detection or other factors) would probably be favored.

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4 CLASSIFICATION

Histopathologic classifications of disease must fulfill two related but disparate roles. One is to provide an assessment of the potential behavior of a lesion to assist the clinician in instituting appropriate treatment and the other is to provide a morphologic framework for understanding pathogenesis. To successfully accomplish the clinical objective, the classification must contain diagnostic categories that correspond to the various therapeutic options; that is to say, a classification with a large number of diagnostic categories based on subtle morphologic differences that are all treated the same way does not serve a useful purpose from a clinical managerial standpoint. Since the therapeutic choices are usually more limited than the morphologic categories, in this scenario, fewer are better. On the other hand, when investigators are trying to elucidate the pathogenesis of a disease process, combining what may be different entities into one category could mask important underlying differences. In this scenario, more is better. Thus, there is an underlying tension between the competing needs of clinical application and research.

In addition to the balance that must be struck between the clinical and research objectives of a histopathologic classification, it is also recognized that with increased understanding of the disease process there is inevitably a need to modify and change the classification. In the past, changes have occurred within the context of morphology, but now it is clear that morphologic taxonomy will metamorphose into a morphologic and molecular genetic taxonomy. For example, recent discussions about the respective roles of cytology and human papillomavirus (HPV) testing in cervical cancer screening have questioned how best to integrate HPV testing (a molecular genetic assay) with cytopathologic diagnoses. Specifically, should these two modalities be reported separately or should they be combined into a single diagnosis based on the results of both tests? It has been demonstrated that the behavior of lesions classified on cytology as atypical squamous cells of undetermined significance (ASC-US) in which high-risk HPV types (ASC-US [HPV-positive]) are detected is the same as lesions classified on cytology as low-grade squamous intraepithelial lesion (LSIL). It appears that the ASC-US (HPV-positive) lesion is, in essence, a LSIL but lacks sufficient morphologic expression to qualify for that diagnosis on cytologic grounds (1). Since in all other respects ASC-US (HPV-positive) resembles LSIL, many investigators believe it should be classified as such. In other words, the morphologic findings should be combined with the molecular findings in arriving at a final diagnosis.

Issues such as this will continue to arise as the molecular characteristics of neoplasms and preneoplastic lesions are elucidated. Ultimately, a new approach to classification that combines histopathology with molecular genetics will emerge. Indeed, classifications will continue to evolve and change; classifications should not, and can not, be embalmed. To do so makes them irrelevant. Evolution, however, is not revolution. Changes to classifications have profound and widespread effects and therefore must be done in a careful, measured fashion. The histopathologic classification of cervical disease is no exception and we have attempted to follow these precepts in this text.

One of the stated goals of this series of Fascicles is to integrate cytology and histopathology. Accordingly, the gamut of squamous lesions that are regarded as precursors of squamous carcinoma of the cervix are termed squamous intraepithelial lesions (SILs). This approach uses the nomenclature of the Bethesda System developed for cytology for histopathologic classification as well. SILs represent alterations in the cervical transformation zone induced by HPV infection and were formerly termed dysplasia (mild, moderate, severe) and carcinoma in situ (CIS) or cervical intraepithelial neoplasia (CIN) and graded CIN 1, 2, and 3. In the late

1970s, some investigators popularized the term "flat condyloma" and advocated separation of these lesions from what were believed to be true cancer precursors, namely CIN 1, based on the notion that flat condylomas were manifestations of banal HPV infection and were not related to cervical carcinoma (9). Subsequently, it was shown that the distinction of flat condyloma and CIN 1 was not reproducible and that both comprise a morphologic continuum attributable to a common etiologic agent, namely HPV (17). Recent morphologic, virologic, and epidemiologic studies have reinforced the view that the development of cervical cancer begins with HPV infection which, if it persists, can lead to malignant transformation (16). Since HPV infections spontaneously regress in most cases and bona fide precursors have a high risk of progression to invasive cancer, the former lesions are generally not treated while the latter are ablated.

In keeping with the approach that diagnostic categories should correspond to therapeutic options and since the most recent investigations confirm that intraepithelial lesions reflect a bimodal disease process (infection and neoplasia), a binary classification is in order. This approach has been embraced by cytopathologists who have made the transition to a binary system (the Bethesda System), which divides SILs into low-grade (LSIL) and high-grade (HSIL), using cytologic criteria (11). The adoption of a binary classification in diagnostic surgical pathology has been more controversial and recently debated (2,10). Introduction of a binary system to histopathology is more problematic than in cytopathology because the traditional histologic classification of preinvasive squamous cervical lesions has been based almost exclusively on architectural as opposed to cytologic features. Specifically, the grading employed in the dysplasia/CIS or the CIN system is based on the extent to which the full thickness of the epithelium is replaced by immature proliferating parabasal cells. Inherent in this approach is the view that these preinvasive lesions progress in a stepwise fashion from low-grade lesions with minimal proliferation to more severe lesions with greater cellular proliferation, and that this corresponds to a progressively increased risk of the development of a direct precursor of invasive cancer. This increase in cellular proliferation is reflected by the level to which proliferative, as opposed to differentiated, cells are located in the squamous epithelium. For purposes of grading, the epithelium is arbitrarily divided into thirds. Lesions in which proliferation is limited to the lower third of the epithelium are designated mild dysplasia (CIN 1), those in which proliferation extends into the middle third are designated moderate dysplasia (CIN 2), and those involving the upper third are designated severe dysplasia or CIS (CIN 3). Implicit in the adoption of a cytologic classification for histology is that cytologic criteria take precedence over architectural criteria.

Adoption of the Bethesda System to histology requires a different approach to grading intraepithelial lesions than what has been employed with the dysplasia/CIS or CIN system. It is not simply a matter of using traditional histologic criteria to grade a lesion as CIN 1, 2, or 3 and then to equate CIN 1 with LSIL and CIN 2 and 3 with HSIL. Although in many instances this method is successful, as discussed in chapter 5, lesions traditionally classified as CIN 2 in the binary system are sometimes classified as low grade. Admittedly, hard data that unequivocally separate an infectious lesion from a cancer precursor are lacking but there is sufficient indirect evidence to support this new approach to histopathologic diagnosis.

A basic tenet in the management of cervical lesions is the need to correlate cytology with colposcopy and histopathology. A common terminology shared by these different modalities simplifies and clarifies communication between the pathologist and the clinician. In this text, we (18) as others (4) advocate the use of a binary histopathologic classification for SILs of the cervix, vagina, and vulva. Because older studies use either dysplasia/CIS or the CIN terminology, in many places in the text we have had to use the older terminology in order to describe the results of these studies. The binary system codifies our current understanding of the pathogenesis of cervical cancer. It could be argued that the use of the term SIL for both the morphologic manifestations of productive HPV infection as well as for direct cancer precursors perpetuates the erroneous notion of a biologic continuum and that more accurate designations would be "HPV infection" for LSIL and "CIN" for HSIL. Although this would be more precise,

the introduction of such terminology at this time would almost certainly lead to confusion among clinicians accustomed to considering cervical cancer precursors as a continuum. In the future, as this concept becomes more familiar to pathologists and clinicians, a change in the terminology would be desirable and appropriate.

Another area where the classification in this text departs from the World Health Organization (WHO) classification (15) is the subject of preinvasive glandular lesions of the endocervix. Unlike the WHO classification, we do not recognize the entity designated "glandular dysplasia." The histologic features of adenocarcinoma in situ (AIS) have been well characterized for many years (3) and it has been recognized that there are glandular lesions that display cytologic atypia and increased proliferation that fall short of AIS. The question that arises is: are these lesions precursors of AIS or are they unrelated benign reactive changes? Proponents of the former view compare the development of preinvasive glandular lesions to that of preinvasive squamous lesions and use the term glandular dysplasia or glandular intraepithelial neoplasia (GIN) (5,6). An understanding of the biology of HPV infection clarifies the issue. Productive HPV infection is tightly linked to squamous differentiation. Production of viral particles occurs in differentiated squamous cells, leading to the development of LSIL. Productive infection does not occur in cells committed to glandular differentiation and, therefore, a low-grade glandular lesion comparable to LSIL does not exist. Occasionally, dysregulation of early gene expression occurs in these nonpermissive glandular cells, leading to hyperproliferation, which pathologists interpret as severe glandular dysplasia or AIS (13). In situ hybridization studies for HPV have failed to detect HPV in glandular atypias less than AIS (8,14). These studies provide cogent evidence that a low-grade glandular dysplastic lesion that is a precursor of AIS does not exist. We advocate the approach recommended by Lee (7) which is to lower the threshold for the diagnosis of AIS slightly so as to include in this category lesions with slightly less atypia, stratification, and mitotic activity than "classic" AIS. All other nonciliated intraglandular lesions, which fall short of this expanded definition of AIS, are classified as "glandular atypia" and most likely reflect reactive changes.

We have applied the bipartite classification of low-grade and high-grade SILs to the vagina and vulva as well. Recent studies correlating morphologic and molecular features of SILs of the vagina and vulva have shown that high-grade vaginal lesions corresponding to vaginal atypical intraepithelial neoplasia (VaIN) 3 and vulvar intraepithelial neoplasia (VIN) 3 contain high-risk HPV types, almost always HPV 16. In contrast, low-grade vaginal lesions (VaIN 1) contain a heterogeneous distribution of HPVs, including low- and high-risk types, resembling the distribution in the cervix. Low-grade vulvar lesions (VIN 1), although also containing a heterogeneous distribution of HPV types, much more frequently contain low-risk HPVs, nearly always HPV 6 or 11 (12). Nonetheless, the occasional presence of high-risk HPVs in these lesions justifies adopting the low- and high-grade terminology for these lesions as well. In all other respects, the classification used in this text for squamous and glandular carcinomas, mesenchymal tumors, and tumor-like lesions corresponds to the WHO classification.

HISTOLOGIC CLASSIFICATION OF TUMORS AND TUMOR-LIKE LESIONS

Uterine Cervix	
1.0	Epithelial Tumors and Related Lesions
1.1	Squamous lesions
1.1.2	Condyloma acuminatum
1.1.3.	Squamous metaplasia
1.1.4	Transitional metaplasia
1.1.5	Squamous atypia
1.1.6	Squamous intraepithelial lesions
1.1.6.1	Low-grade squamous intraepithelial lesion (LSIL) Cervical intraepithelial neoplasia (ClN) 1, mild dysplasia
1.1.6.2	High-grade squamous intraepithelial lesion (HSlL) ClN 2, moderate dysplasia, ClN 3, severe dysplasia/ carcinoma in situ
1.1.7	Squamous cell carcinoma[a]
1.1.7.1	Keratinizing
1.1.7.2	Nonkeratinizing
1.1.7.3	Verrucous
1.1.7.4	Warty (condylomatous)
1.1.7.5	Papillary (squamous transitional)
1.1.7.6	Lymphoepithelioma-like
1.2	Glandular lesions
1.2.1	Endocervical polyp

- 1.2.2 Müllerian papilloma
- 1.2.3 Tunnel clusters
- 1.2.4 Endocervical glandular hyperplasia
- 1.2.5 Microglandular hyperplasia
- 1.2.6 Mesonephric hyperplasia
- 1.2.7 Arias-Stella reaction
- 1.2.8 Endometriosis
- 1.2.9 Tubal, tuboendometrioid, endometrioid metaplasia
- 1.2.10 Endocervicosis
- 1.2.11 Cysts
- 1.2.12 Intestinal metaplasia
- 1.2.13 Atypical oxyphilic metaplasia
- 1.2.14 Ectopic prostate tissue
- 1.2.15 Glandular atypia
- 1.2.16 Adenocarcinoma in situ
- 1.2.17 Adenocarcinoma[b]
  - 1.2.17.1 Endocervical adenocarcinoma, usual type
  - 1.2.17.2 Mucinous
  - 1.2.17.3 Endometrioid
  - 1.2.17.4 Well-differentiated villoglandular adenocarcinoma
  - 1.2.17.5 Clear cell
  - 1.2.17.6 Minimal deviation (adenoma malignum)
  - 1.2.17.7 Serous
  - 1.2.17.8 Mesonephric
- 1.3 Other epithelial tumors
  - 1.3.1 Adenosquamous carcinoma
  - 1.3.2 Glassy cell carcinoma
  - 1.3.3 Adenoid cystic carcinoma
  - 1.3.4 Adenoid basal tumors
    - 1.3.4.1 Adenoid basal epithelioma
    - 1.3.4.2 Adenoid basal carcinoma
  - 1.3.5 Neuroendocrine tumors
    - 1.3.5.1 Typical carcinoid tumor
    - 1.3.5.2 Atypical carcinoid
    - 1.3.5.3 Small cell carcinoma
    - 1.3.5.4 Large cell neuroendocrine carcinoma
  - 1.3.6 Undifferentiated carcinoma

2.0 Mesenchymal Tumors
- 2.1 Mesodermal stromal polyp
- 2.2 Leiomyoma
- 2.3 Other benign mesenchymal tumors
- 2.4 Leiomyosarcoma
- 2.5 Endometrioid stromal sarcoma (low-grade)
- 2.6 Undifferentiated endocervical stromal sarcoma
- 2.7 Sarcoma botryoides (embryonal rhabdomyosarcoma)
- 2.8 Alveolar soft-part sarcoma
- 2.9 Osteosarcoma
- 2.10 Other malignant mesenchymal tumors

3.0 Mixed Epithelial and Mesenchymal Tumors
- 3.1 Papillary adenofibroma
- 3.2 Adenomyoma
- 3.3 Adenosarcoma
- 3.4 Malignant mixed mesodermal tumor (carcinosarcoma)
- 3.5 Wilms tumor

4.0 Miscellaneous Tumors
- 4.1 Melanocytic nevus
- 4.2 Blue nevus
- 4.3 Malignant melanoma
- 4.4 Glomus tumor
- 4.5 Lymphoma and leukemia
- 4.6 Tumors of germ cell type
  - 4.6.1 Mature teratoma
  - 4.6.2 Yolk sac tumor

5.0 Secondary Tumors

6.0 Tumor-Like Lesions
- 6.1 Epidermal metaplasia
- 6.2 Lymphoma-like lesion
- 6.3 Decidual nodule
- 6.4 Placental site nodule
- 6.5 Amputation (traumatic) neuroma
- 6.6 Postoperative spindle cell nodule
- 6.7 Glial polyp

Vagina

1.0 Epithelial Tumors and Related Lesions
- 1.1 Squamous lesions
  - 1.1.1 Squamous papilloma
  - 1.1.2 Condyloma acuminatum
  - 1.1.3 Transitional metaplasia
  - 1.1.4 Squamous atypia
  - 1.1.5 Squamous intraepithelial lesions
    - 1.1.5.1 Low-grade squamous intraepithelial lesion
      Vaginal intraepithelial neoplasia (VaIN) 1, mild dysplasia
    - 1.1.5.2 High-grade squamous intraepithelial lesion, VaIN 2, moderate dysplasia, VaIN 3, severe dysplasia/carcinoma in situ
  - 1.1.6 Squamous cell carcinoma
    - 1.1.6.1 Keratinizing
    - 1.1.6.2 Nonkeratinizing
    - 1.1.6.3 Verrucous
    - 1.1.6.4 Warty (condylomatous)
- 1.2. Glandular lesions
  - 1.2.1 Adenosis
  - 1.2.2 Atypical adenosis
  - 1.2.3 Endometriosis
  - 1.2.4 Endocervicosis
  - 1.2.5 Cysts
  - 1.2.6 Müllerian papilloma
  - 1.2.7 Adenocarcinoma
    - 1.2.7.1 Endometrioid, endocervical and intestinal types
    - 1.2.7.2 Clear cell
    - 1.2.7.3 Mesonephric
- 1.3 Other epithelial tumors
  - 1.3.1 Adenosquamous carcinoma
  - 1.3.2 Miscellaneous tumors
    - 1.3.2.1 Adenoid basal carcinoma
    - 1.3.2.2 Adenoid cystic carcinoma

- 1.3.2.3 Carcinoid tumor
- 1.3.2.4 Small cell carcinoma
- 1.3.2.5 Undifferentiated carcinoma

2.0 Mesenchymal Tumors
- 2.1 Mesodermal stromal polyp
- 2.2 Leiomyoma
- 2.3 Rhabdomyoma
- 2.4 Other benign mesenchymal tumors
- 2.5 Leiomyosarcoma
- 2.6 Sarcoma botryoides (embryonal rhabdomyosarcoma)
- 2.7 Endometrioid stromal sarcoma
- 2.8 Other malignant mesenchymal tumors

3.0 Mixed Epithelial and Mesenchymal Tumors
- 3.1 Mixed tumor
- 3.2 Mixed tumor resembling synovial sarcoma
- 3.3 Adenosarcoma
- 3.4 Malignant mixed mesodermal tumor (carcinosarcoma)

4.0 Miscellaneous Tumors
- 4.1 Melanocytic nevus
- 4.2 Blue nevus
- 4.3 Malignant melanoma
- 4.4 Yolk sac tumor
- 4.5 Mature cystic teratoma
- 4.6 Adenomatoid tumor
- 4.7 Villous adenoma
- 4.8 Malignant lymphoma and other lymphohistiocytic lesions
- 4.9 Primitive neuroectodermal tumor

5.0 Secondary Tumor

6.0 Tumor-Like Lesions
- 6.1 Postoperative spindle-cell nodule
- 6.2 Vault granulation tissue
- 6.3 Prolapsed fallopian tube
- 6.4 Malakoplakia
- 6.5 Lymphoma-like lesion

Vulva

1.0 Epithelial Tumors
- 1.1 Benign epithelial tumors
  - 1.1.1 Squamous (vestibular) papilloma
  - 1.1.2 Fibroepithelial polyp
  - 1.1.3 Condyloma acuminatum
  - 1.1.4 Seborrheic keratosis
  - 1.1.5 Epidermolytic acanthoma
  - 1.1.6 Keratoacanthoma
  - 1.1.7 Folliculosebaceous cystic hamartoma
  - 1.1.8 Trichofolliculoma
- 1.2 Squamous intraepithelial lesions
  - 1.2.1 Low-grade squamous intraepithelial lesion (LSIL)
    Vulvar intraepithelial neoplasia (VIN) 1, mild dysplasia
  - 1.2.2 High-grade squamous intraepithelial lesion (HSIL)
    VIN 2, moderate dysplasia, VIN 3, severe dysplasia, carcinoma in situ[c]
- 1.3 Squamous cell carcinoma[d]
  - 1.3.1 Usual type
  - 1.3.2 Basaloid
  - 1.3.3 Warty (condylomatous)
  - 1.3.4 Squamous cell carcinoma with giant cells
  - 1.3.5 Spindle cell squamous carcinoma (squamous cell carcinoma with sarcomatoid features)
  - 1.3.6 Adenoid squamous
  - 1.3.7 Lymphoepithelioma-like
- 1.4 Verrucous
- 1.5 Basal cell
  - 1.5.1 Adenoid basal
  - 1.5.2 Metatypical basal cell
  - 1.5.3 Sebaceous
  - 1.5.4 Mixed carcinoma
- 1.6 Glandular lesions
  - 1.6.1 Papillary hidradenoma
  - 1.6.2 Nodular (clear cell) hidradenoma
  - 1.6.3 Syringoma
  - 1.6.4 Mixed tumor of the vulva
  - 1.6.5 Trichoepithelioma
  - 1.6.6 Trichilemmoma
  - 1.6.7 Adenoma of minor vestibular glands
  - 1.6.8 Paget disease and Paget-like lesions
    - 1.6.8.1 Primary cutaneous Paget disease, intraepithelial
    - 1.6.8.2 Primary cutaneous Paget disease, invasive
    - 1.6.8.3 Paget disease secondary to rectal or anal adenocarcinoma
    - 1.6.8.4 Paget-like disease secondary to urothelial neoplasia
  - 1.6.9 Bartholin gland tumors
    - 1.6.9.1 Adenocarcinoma
    - 1.6.9.2 Squamous cell carcinoma
    - 1.6.9.3 Adenoid cystic carcinoma
    - 1.6.9.4 Adenosquamous carcinoma
    - 1.6.9.5 Transitional cell carcinoma
  - 1.6.10 Malignant mixed tumor
  - 1.6.11 Mammary-like carcinoma and other mammary-like tumors
  - 1.6.12 Adenocarcinoma of cloacogenic origin
  - 1.6.13 Carcinoma of sweat gland origin
  - 1.6.14 Mucinous eccrine carcinoma with neuroendocrine differentiation
  - 1.6.15 Mucinous adenocarcinoma with focal squamous and neuroendocrine differentiation

2.0 Mesenchymal Tumors
- 2.1 Benign mesenchymal tumors
  - 2.1.1 Lipoma/fibrolipoma
  - 2.1.2 Intradermal spindle cell/pleomorphic lipoma
  - 2.1.3 Lipoblastoma-like tumor
  - 2.1.4 Nevus lipomatosis superficialis
  - 2.1.5 Hemangioma
    - 2.1.5.1 Capillary
    - 2.1.5.2 Cavernous
    - 2.1.5.3 Acquired
  - 2.1.6 Angiokeratoma

- 2.1.7 Pyogenic granuloma
- 2.1.8 Lymphoid hamartoma
- 2.1.9 Cellular angiofibroma
- 2.1.10 Superficial angiomyxoma
- 2.1.11 Angiomyofibroblastoma
- 2.1.12 Aggressive angiomyxoma
- 2.1.13 Lymphangioma
- 2.1.14 Lymphangioma circumscriptum
- 2.1.15 Fibroma
- 2.1.16 Solitary fibrous tumor
- 2.1.17 Giant cell angiofibroma
- 2.1.18 Leiomyoma
- 2.1.19 Atypical leiomyoma
- 2.1.20 Granular cell tumor
- 2.1.21 Neurofibroma
- 2.1.22 Schwannoma (neurilemoma)
- 2.1.23 Paraganglioma
- 2.1.24 Glomus tumor
- 2.1.25 Benign fibrous histiocytoma
- 2.1.26 Atypical fibrous histiocytoma
- 2.1.27 Rhabdomyoma

- 2.2 Malignant mesenchymal tumors
  - 2.2.1 Embryonal rhabdomyosarcoma (sarcoma botryoides)
  - 2.2.2 Alveolar rhabdomyosarcoma
  - 2.2.3 Alveolar soft-part sarcoma
  - 2.2.4 Leiomyosarcoma
  - 2.2.5 Dermatofibrosarcoma protuberans
  - 2.2.6 Composite tumor consisting of dermatofibrosarcoma protuberans and giant cell fibroblastoma
  - 2.2.7 Malignant fibrous histiocytoma
  - 2.2.8 Fibrosarcoma
  - 2.2.9 Angiomyofibrosarcoma
  - 2.2.10 Synovial sarcoma
  - 2.2.11 Epithelioid sarcoma
  - 2.2.12 Malignant rhabdoid tumor
  - 2.2.13 Malignant schwannoma
  - 2.2.14 Lymphangiosarcoma
  - 2.2.15 Angiosarcoma
  - 2.2.16 Kaposi sarcoma
  - 2.2.17 Hemangiopericytoma
  - 2.2.18 Liposarcoma
  - 2.2.19 Malignant granular cell tumor

- 3.0 Melanocytic Tumors
  - 3.1 Congenital melanocytic nevus
  - 3.2 Common acquired melanocytic nevus
  - 3.3 Lentigo simplex
  - 3.4 Melanosis
  - 3.5 Blue nevus
  - 3.6 Atypical melanocytic nevus of genital type
  - 3.7 Dysplastic melanocytic nevus
  - 3.8 Malignant melanoma
  - 3.9 Malignant blue nevus

- 4.0 Miscellaneous Tumors
  - 4.1 Malignant lymphoma
  - 4.2 Tumors of germ cell type
    - 4.2.1 Yolk sac tumor (endodermal sinus tumor)
  - 4.3 Neuroendocrine and neuroectodermal tumors
    - 4.3.1 Merkel cell tumor
    - 4.3.2 Peripheral neuroectodermal tumor

- 5.0 Secondary Tumors

- 6.0 Tumor-Like Lesions and Non-neoplastic Disorders
  - 6.1 Pseudoepitheliomatous hyperplasia
  - 6.2 Endometriosis
  - 6.3 Decidua
  - 6.4 Langerhans cell histiocytosis
  - 6.5 Benign xanthogranuloma
  - 6.6 Verruciform xanthoma
  - 6.7 Desmoid tumor
  - 6.8 Sclerosing lipogranuloma
  - 6.9 Nodular fascitis
  - 6.10 Postoperative spindle cell nodule
  - 6.11 Crohn disease
  - 6.12 Vulvitis granulomatosa
  - 6.13 Cysts
    - 6.13.1 Bartholin duct
    - 6.13.2 Mucinous
    - 6.13.3 Epidermal (keratinous)
    - 6.13.4 Mesonephric-like
    - 6.13.5 Ciliated
    - 6.13.6 Mesothelial
    - 6.13.7 Periurethral
  - 6.14 Other epithelial disorders of skin and mucosa
    - 6.14.1 Lichen sclerosus
    - 6.14.2 Squamous cell hyperplasia
    - 6.14.3 Other dermatoses

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[a]For purposes of staging and treatment, the International Federation of Gynecologists and Obstetricians subdivides squamous cell carcinoma into microinvasive and frankly invasive carcinomas.

[b]Includes frankly invasive adenocarcinoma and so-called microinvasive adenocarcinoma (early invasive adenocarcinoma).

[c]Includes differentiated VIN.

[d]For purposes of clinical management, squamous cell carcinoma is subdivided into superficially invasive and frankly invasive carcinomas.

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5 TUMORS OF THE CERVIX

SQUAMOUS LESIONS

Squamous Papilloma

Definition. *Squamous papilloma* is a benign papillary lesion consisting of a fibrovascular stalk covered by mature squamous epithelium. *Fibroepithelial polyp* typically contains more fibrous tissue than the squamous papilloma, but for practical purposes, this term and *ectocervical polyp* are synonymous with squamous papilloma.

General Features. Squamous papillomas are usually solitary, arise on the ectocervix or the squamocolumnar junction, and range in diameter from a few millimeters to 2 cm. In one study, they were found in 0.4 percent of cervical biopsy specimens (138). Squamous papillomas are less common on the cervix than in the vagina or vulva.

Microscopic Findings. Squamous papillomas have a thick, central fibrovascular core and smaller branching fibrovascular papillae covered by mature squamous epithelium that is not cytologically atypical (see fig. 6-1). In the older literature, squamous papillomas of the cervix were included with condylomata acuminata as papillomas of the cervix (207,255). Although the venereal and viral natures of condylomas were appreciated, condylomas and squamous papillomas were considered indistinguishable morphologically. Subsequently, koilocytotic atypia, also termed koilocytosis, was recognized as a marker for human papillomavirus (HPV) infection in the lower genital tract, and molecular virologic studies unequivocally demonstrated the presence of HPV in condylomas (134,322). In contrast, koilocytotic atypia is not a feature of squamous papillomas, and molecular virologic examination of similar lesions on the vulva has failed to demonstrate HPV (38,322). The different etiology of squamous papillomas and condylomas has obvious clinical significance, but the differential diagnosis may be difficult. The most useful diagnostic feature is the presence of koilocytotic atypia in the condyloma; however, this finding may be subtle or absent in some condylomas, in which case the architectural features assist in the diagnosis. Subtle evidence of koilocytosis in lesions suspected of being condylomas should be searched for in the clefts of squamous epithelium between rounded or spiked excrescences near the surface. Squamous papilloma contains a central fibrovascular stalk and does not show the marked degree of arborization characteristic of condyloma acuminatum.

Treatment. Squamous papillomas do not require treatment. Usually the diagnostic biopsy removes the entire lesion.

Condyloma Acuminatum

Definition. *Condyloma acuminatum* is a papillary, exophytic, benign neoplasm caused by HPV.

General Features. HPV types 6 and 11 are found in 70 to 90 percent of condyloma acuminatum lesions, but occasionally, other types, including type 16, are present. Multiple condylomas are not common on the cervix; they are much more frequently encountered on the vulva. In one population-based study, the frequency of multiple condylomas in various parts of the female genital tract was as follows: vulva, 66 percent; vagina, 37 percent; perineum, 29 percent; anus, 23 percent; cervix, 8 percent; and urethra, 4 percent (67). Condyloma acuminatum is discussed in greater detail in chapter 7.

Gross Findings. Cervical condylomas have an exophytic, spiked, or cauliflower-like appearance (fig. 5-1). Colposcopically, after application of 3 to 5 percent acetic acid, they appear white and have typical vascular patterns because of the rich vascular supply that terminates near the tips of the papillary fronds.

Microscopic Findings. Condyloma acuminatum is characterized by acanthotic squamous epithelium overlying delicate fibrovascular cores (fig. 5-2). The surface squamous epithelium often has an undulating appearance because of the presence of multiple round or blunted

Figure 5-1

CONDYLOMA ACUMINATUM

Colposcopic view reveals exophytic, white lesions with surface papillary projections on the ectocervical mucosa and in the vaginal fornix.

excrescences. Accompanying the exophytic growth is marked papillomatosis, characterized by a downward proliferation of anastomosing rete pegs. Within the papillary fronds are an increased number of capillaries, and as a result, there may be only a few layers of squamous epithelial cells between the capillaries and the surface. The squamous epithelium typically exhibits hyperkeratosis and hypergranulosis. Mitotic activity is confined to the basal and parabasal layers but may appear close to the surface where the stromal papillae extend (figs. 5-2, 5-3).

Although koilocytosis is pathognomonic for condyloma acuminatum, it may be focal or absent in a single section of an otherwise typical condyloma. Deeper sections may assist in identifying koilocytosis. When koilocytosis is absent, characteristic architectural features can be used to diagnose the lesion as a condyloma; demonstration of increased proliferative activity, as assessed by immunohistochemical expression of Ki-67 (MIB-1) can be used to support the diagnosis (fig. 5-3) (319). Proliferative activity is identified above the parabasal layer, extending into the intermediate layer, with zones of greater and lesser activity within different regions of the papillae. Identification of low-risk HPV types (most commonly 6 and 11) within the lesion by in situ hybridization confirms the diagnosis of condyloma (fig. 5-3). When foci exhibiting decreased maturation, moderate to marked nuclear atypia, and increased mitotic activity are identified, these areas should be diagnosed as high-grade squamous intraepithelial lesion (HSIL) arising within the condyloma, and graded as a flat cervical lesion.

Cytologic Findings. HPV-induced viral cytopathic changes (koilocytosis) are characterized by mild nuclear enlargement and nuclear hyperchromasia, nuclear membrane irregularities, binucleation and multinucleation, and cytoplasmic clearing. These changes are typically focal and most often localized to the clefts between papillae.

Treatment and Prognosis. Condylomas are benign, although occasionally a squamous cell carcinoma develops within a condyloma (48, 364). Condylomas may spontaneously regress or persist for many years. The natural history of condylomas is related in part to the immune status of the patient (153). Small lesions can be removed by excisional biopsy and cryosurgery; laser vaporization is used for larger lesions. Recently, treatment using immune modulators has been introduced (see chapter 7).

Squamous Metaplasia

Definition. *Squamous metaplasia* is the replacement of endocervical epithelium by undifferentiated subcolumnar reserve cells, which differentiate into squamous epithelium. The process by which endocervical epithelium is replaced by squamous epithelium to form the transformation zone of the cervix is discussed in chapter 2.

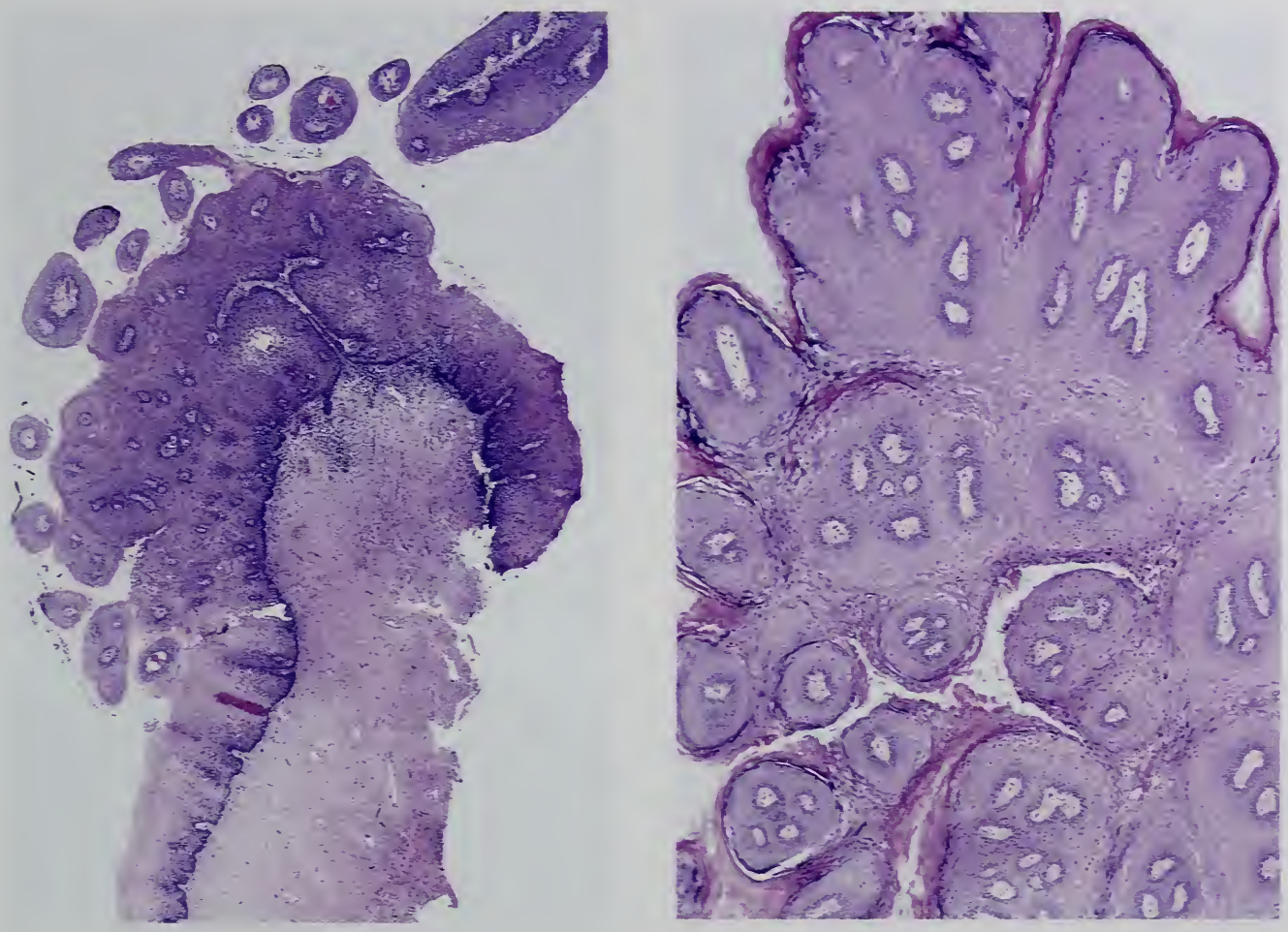


Figure 5-2

CONDYLOMA ACUMINATUM

Left: An exophytic papillary lesion is adjacent to flat normal squamous mucosa.
Right: Papillary fronds are covered by acanthotic, hyperkeratotic squamous epithelium.

Microscopic Findings. Squamous metaplasia is characterized early in its development by stratified, undifferentiated, so-called reserve cells, which proliferate immediately beneath the columnar epithelium. The reserve cells are cuboidal to low columnar (fig. 5-4), with round to oval nuclei and scant cytoplasm. Reserve cells eventually acquire more abundant eosinophilic cytoplasm as they mature into squamous epithelial cells. The metaplastic squamous epithelium lacks intracytoplasmic glycogen, which permits its distinction from the native squamous epithelium. In addition, unlike native squamous epithelium, metaplastic squamous epithelium overlies endocervical glands. Typically, metaplastic squamous epithelium replaces the endocervical epithelium on the surface and extends into the endocervical glandular clefts.

Cytologic Findings. In cytologic preparations, metaplastic cells are smaller than intermediate and superficial cells and thus have a higher nuclear-cytoplasmic ratio. The cells are oval in shape. They are less polygonal than mature cells and contain oval nuclei with even chromatin and occasionally evident nucleoli. The cytoplasm is dense and cyanophilic (fig. 5-5).

Differential Diagnosis. Metaplastic squamous epithelium that becomes glycogenated can be misinterpreted as koilocytosis and therefore erroneously classified as a low-grade squamous intraepithelial lesion (LSIL). In contrast to the koilocytosis in LSIL, the nuclei in glycogenated metaplastic squamous epithelium are not enlarged or atypical, and are centrally rather than eccentrically located.

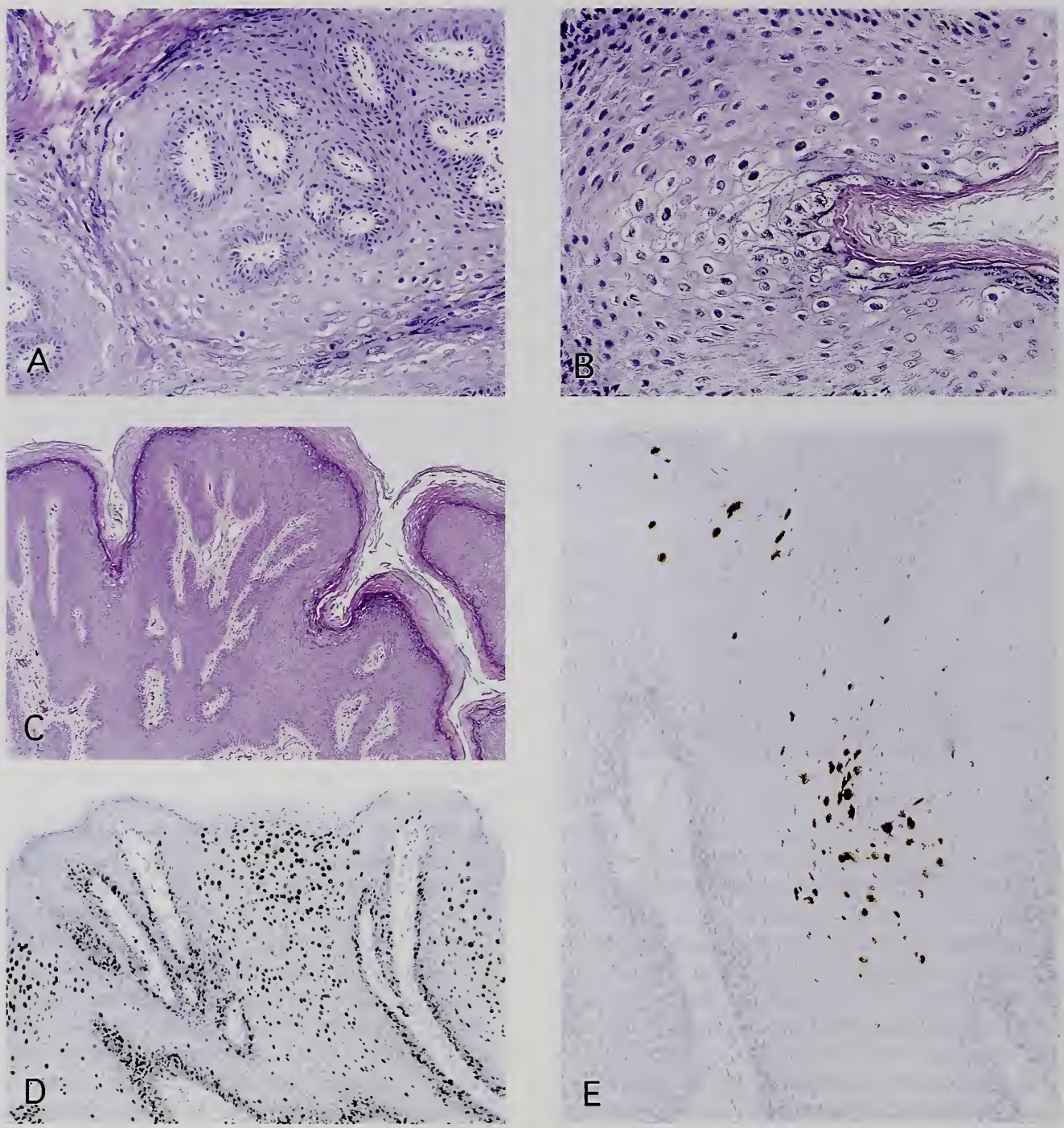


Figure 5-3

CONDYLOMA ACUMINATUM

A: A papilla contains delicate fibrovascular cores. Koilocytosis is confined to the superficial epithelium lining the clefts of adjacent papillae.

B: Acanthotic squamous mucosa with hyperkeratosis and hypergranulosis. Koilocytotic change is evident at the base of the invaginated cleft.

C: A papillary exophytic lesion exhibits acanthosis, hyperkeratosis, and hypergranulosis, but koilocytosis is minimal.

D: Numerous nuclei are positive for Ki-67 within the acanthotic intermediate layer, with marked variation in proliferative activity in different regions of the papillae.

E: In situ hybridization for human papillomavirus (HPV) 6/11 shows the characteristic diffuse brown intranuclear signal associated with productive HPV infection. Only some cells are positive, particularly those clustered in the cleft where koilocytosis is usually most evident.

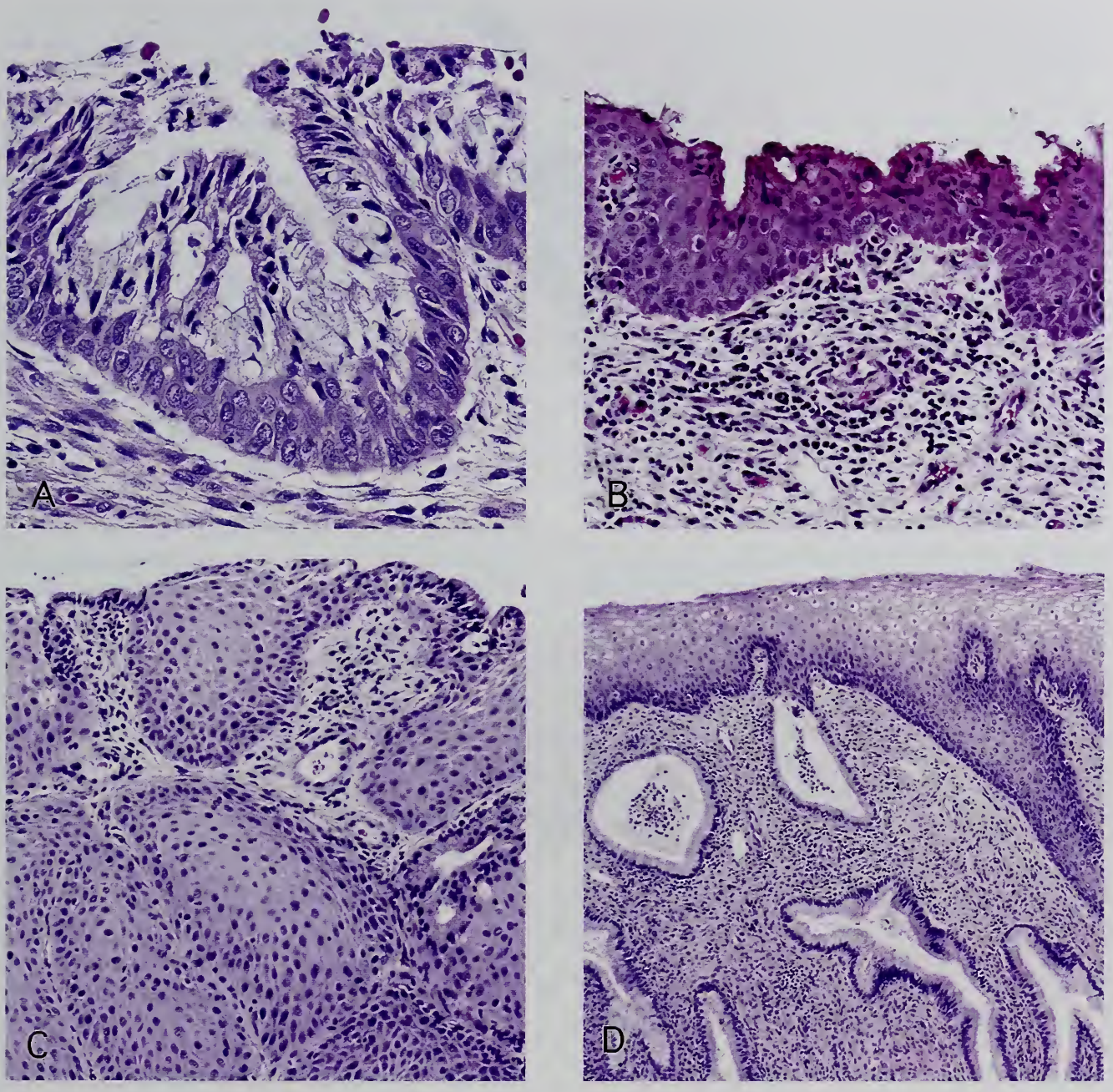


Figure 5-4

SQUAMOUS METAPLASIA

A: Early squamous metaplasia within the cervical transformation zone is characterized by immature squamous cells that differentiate from the reserve cell layer beneath the endocervical glandular epithelium.

B: Early squamous metaplasia within the cervical transformation zone is characterized by immature parabasal type cells with a high nuclear-cytoplasmic ratio. Nuclei are uniform, with delicate chromatin and occasional small nucleoli.

C: Mature squamous epithelium fills the endocervical glands within the transformation zone.

D: The transformation zone is composed of mature squamous metaplastic epithelium overlying endocervical glands and extending into a gland.

Immature squamous metaplasia is characterized by a relatively uniform population of basal type squamous cells with scant cytoplasm and oval nuclei lacking pleomorphism. Maturation may occur near the surface, in which case, cells have more abundant cytoplasm and nuclei are rounder. Although there may be some coarsening of the chromatin, the nuclei are not

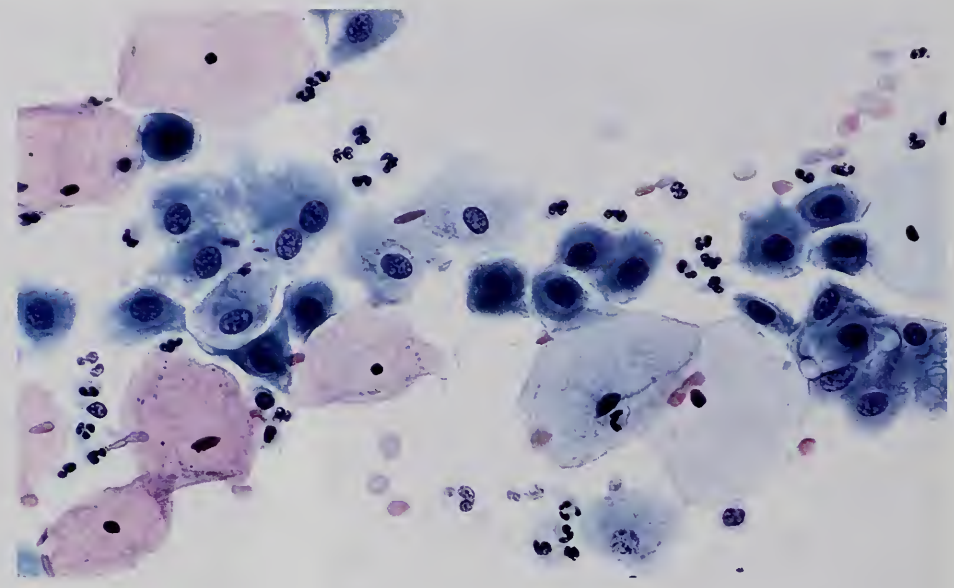


Figure 5-5

SQUAMOUS METAPLASIA

Polygonal cells with dense cytoplasm have an increased nuclear-cytoplasmic ratio compared with intermediate and superficial cells; the nuclei are oval with uniformly dispersed chromatin.

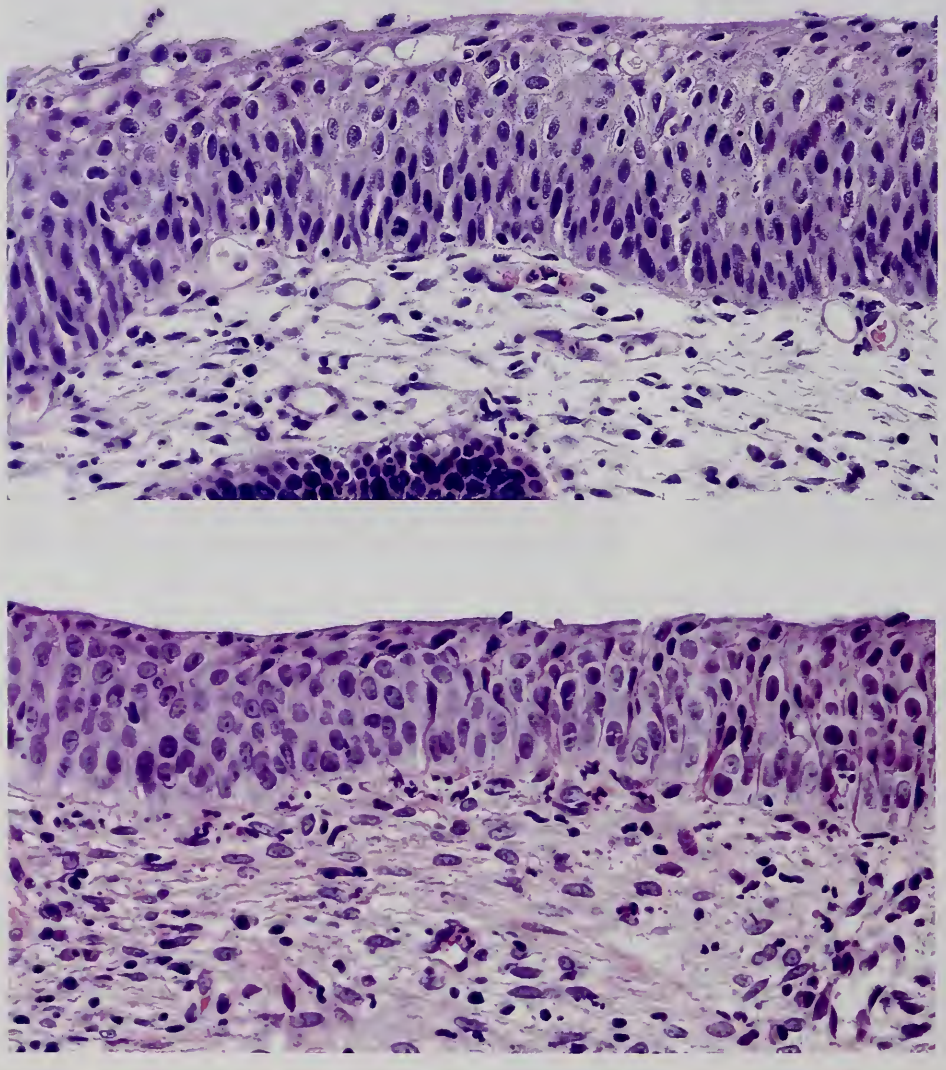


Figure 5-6

ATYPICAL IMMATURE SQUAMOUS METAPLASIA

Top: Immature metaplastic epithelium contains irregularly shaped nuclei, suggesting the possibility of a high-grade squamous intraepithelial lesion (HSIL), but nuclear crowding and overlapping are absent. Polymerase chain reaction (PCR) analysis failed to detect HPV and thus this lesion likely represents immature metaplasia.

Bottom: Lack of maturation in metaplastic epithelium suggests the possibility of HSIL, but the nuclei have uniform chromatin and nucleoli. HSIL was present near this excisional biopsy specimen.

hyperchromatic and the nuclear membranes are smooth. There is preservation of polarity, lack of crowding, and absence of cellular disorganization in the deeper layers. Although mitotic figures may be evident, sometimes even close to the surface, abnormal mitotic figures are rarely, if ever, observed. The presence of a layer of mucinous epithelium on the surface, representing the last remnant of endocervical epithelium that is being replaced by the metaplastic squamous epithelium, is useful in distinguishing immature metaplasia from a squamous intraepithelial lesion because mucinous epithelium rarely overlies an intraepithelial lesion (fig. 5-4A).

Immature squamous metaplasia may exhibit nuclear atypia. The original report of a lesion termed *atypical immature metaplasia* (88) described immature squamous proliferations having some features of condyloma acuminatum. Subsequent studies have used this designation for immature squamous metaplastic lesions suggestive of HSIL but lacking sufficient nuclear atypia and mitotic activity for definitive diagnosis (125,311). It appears that atypical immature metaplasia is not a specific entity but rather a group of morphologically equivocal lesions comprising true HPV-related HSIL and true immature metaplasia. Evidence of almost any degree of mitotic activity, of atypical mitotic figures, or of any degree of cellular disarray or nuclear pleomorphism favors a diagnosis of HSIL rather than immature or atypical immature squamous metaplasia. In contrast to HSIL, the nuclei of immature metaplasia cells are only slightly enlarged and round with finely granular chromatin, and often have evident nucleoli (fig. 5-6). Additional levels and immunohistochemical evaluation of proliferative activity (Ki-67) and p16 expression can resolve most cases (see discussion of HSIL below).

Immature metaplasia also can exhibit papillary growth, suggesting HSIL or papillary squamous cell carcinoma in situ (fig. 5-7). Some examples may represent immature metaplasia involving papillary areas of the transformation zone, unrelated to HPV infection, but many examples of papillary immature metaplasia represent immature condyloma related to low-risk HPV infection (405a,422a). As with flat immature squamous metaplasia, immunohistochemical assessment of proliferative activity and p16 expression distinguish these lesions. In both HSIL and papillary squamous cell carcinoma in situ, the Ki-67 proliferation index is notably elevated and p16 expression is diffuse with moderate to strong intensity, whereas metaplasia is characterized by proliferative activity confined to the parabasal layer and p16 expression is patchy and weak or absent. Immature condyloma has some increased proliferative activity but lacks diffuse or strong p16 expression.

Transitional Metaplasia

Another type of metaplasia that may be seen in association with atrophy, and occasionally focally in the absence of atrophy, is *transitional metaplasia*. Almost all cases occur in postmenopausal women: mean ages of 60 and 68 years are reported in the two largest series (102,425).

The lesion usually occurs on the ectocervix but sometimes involves the transformation zone, and less commonly, the vagina. It is composed of basal and parabasal cells, with ovoid nuclei that often contain a longitudinal groove. The process involves the full thickness of the epithelium and resembles transitional epithelium (fig. 5-8). Because of the full-thickness involvement by basal and parabasal cells, this lesion can simulate HSIL. In contrast to HSIL, transitional metaplasia lacks cytologic atypia and mitotic activity. As with immature squamous metaplasia, immunostains for Ki-67 and p16 are useful for differentiating transitional metaplasia from HSIL; the latter lesion is characterized by increased proliferative activity and diffuse p16 expression whereas the former lacks these features.

Immunohistochemical studies reveal that the transitional, glandular, and squamous epithelia of the cervix show distinctive patterns of expression of cytokeratins (CK)13, CK17, CK18, and CK20, supporting the view that the transitional-like epithelium is indeed metaplastic. Moreover, the immunolocalization of CK13, CK17, and CK18 in cervical transitional epithelium is essentially the same as that of normal urothelium. Transitional-like epithelium in the cervix does not express markers of terminal urothelial differentiation, such as CK20 and the asymmetric unit protein (AUM), suggesting that it is an immature form of transitional epithelium (159).

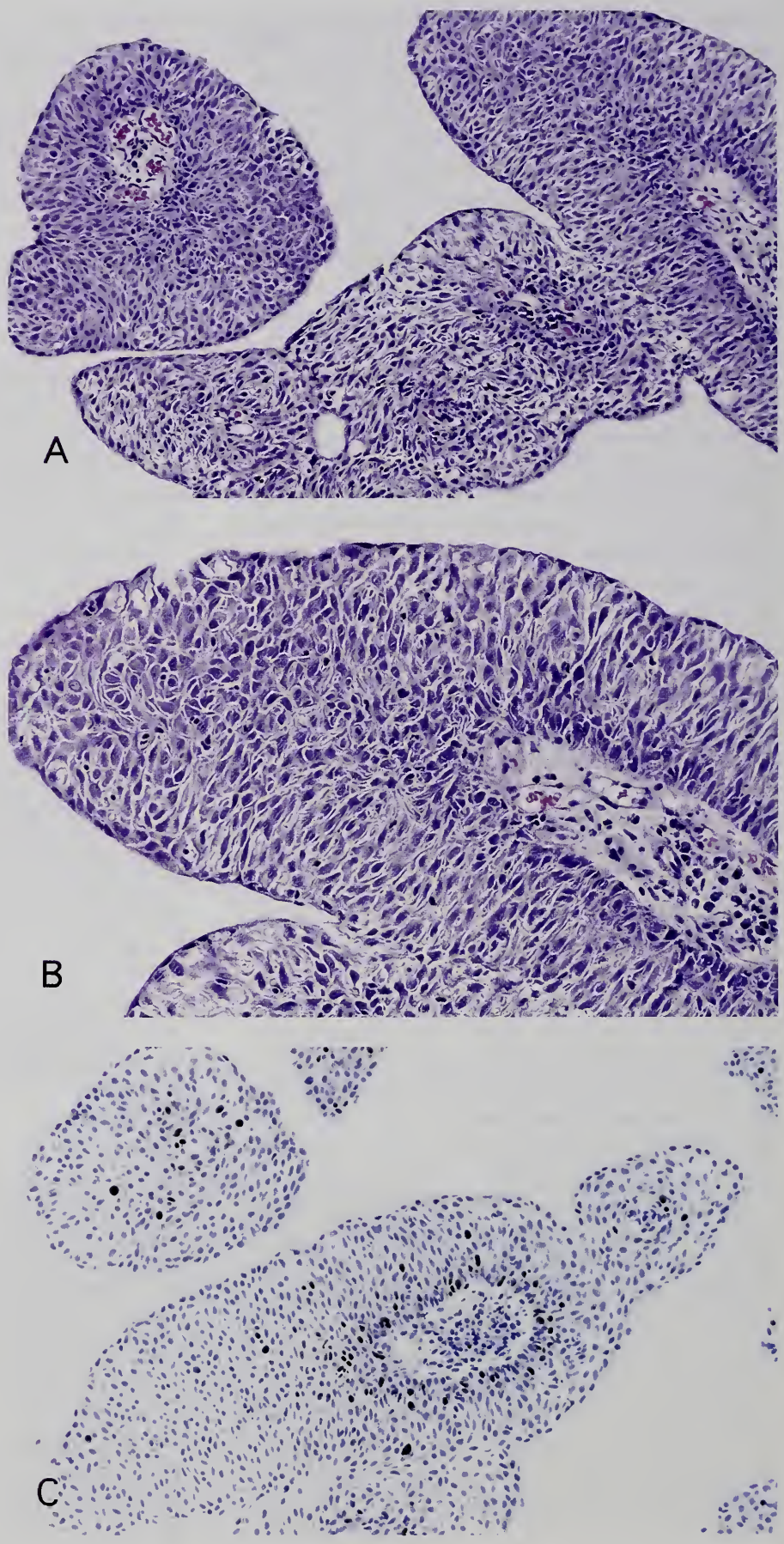


Figure 5-7

PAPILLARY IMMATURE METAPLASIA

A: Papillae are lined by acanthotic immature squamous epithelium, suggesting HSIL at low magnification.

B: Squamous epithelium is immature but the nuclei are uniform and orderly, without pleomorphism or mitotic activity.

C: Immunohistochemical stain for Ki-67 demonstrates minimal proliferative activity, with positive nuclei predominantly confined to the parabasal layer near the fibrovascular core of the papilla.

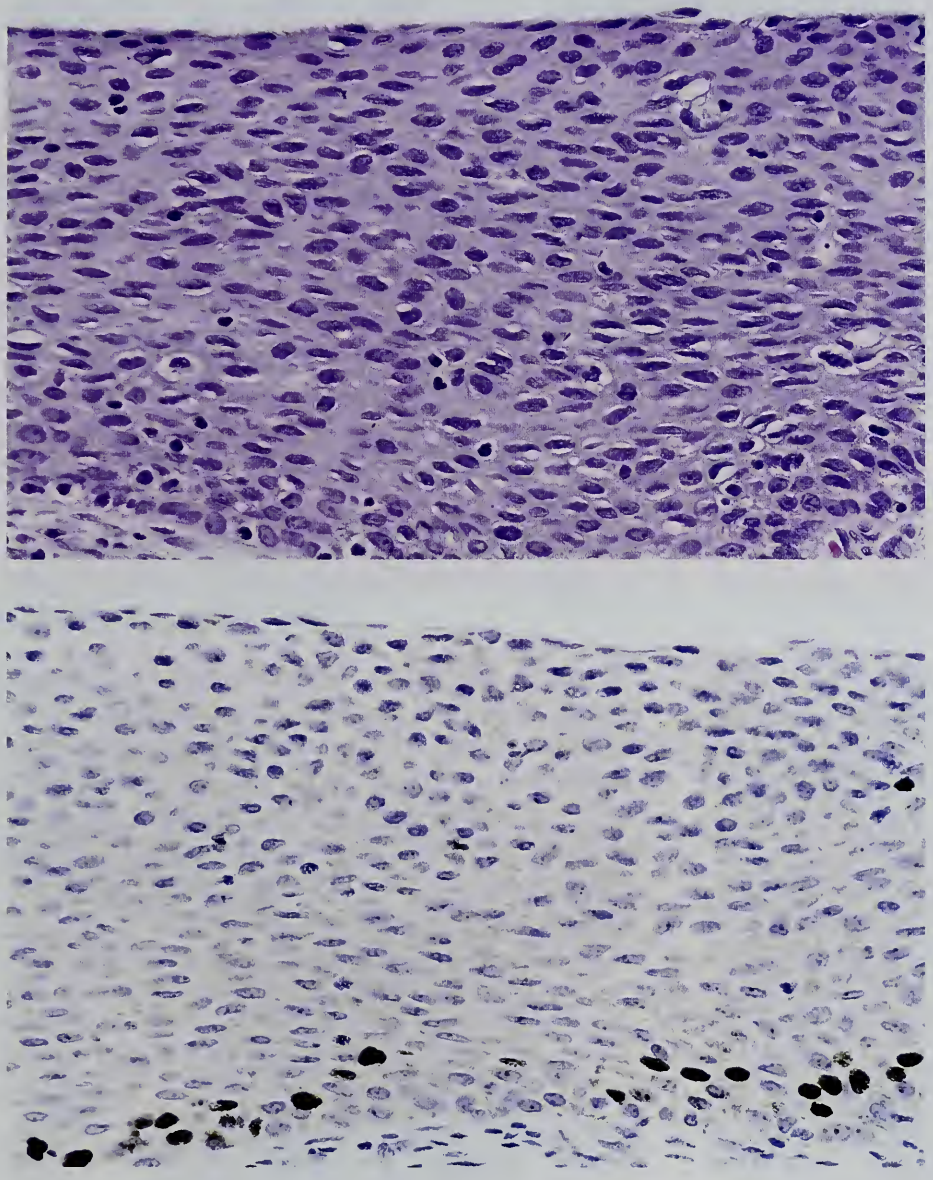


Figure 5-8

TRANSITIONAL METAPLASIA

Top: Immature mucosa contains elongated cells with longitudinally oriented, occasionally grooved, nuclei, simulating urothelium.

Bottom: Minimal Ki-67 proliferative activity is confined to the parabasal layer.

Squamous Atypia

Definition. *Squamous atypia* is occasionally used to describe a lesion characterized by a relatively uniform population of cells with nuclear enlargement and prominent nucleoli. The squamous cells are not crowded and retain an orderly pattern of maturation. This type of atypia is generally attributed to reactive and reparative processes. The term is at times also used to refer to cytologic changes in tissue specimens suggestive of LSIL but qualitatively or quantitatively insufficient for definitive diagnosis, in a fashion analogous to the use of atypical squamous cells of undetermined significance (ASC-US) for cytologic specimens. The use of this term for histologic diagnosis should be minimized as it is not a distinct biologic entity and does not assist in clinical management.

General Features. Squamous atypia usually arises in metaplastic squamous epithelium and may be seen in the absence of other abnormalities or in association with inflammation or ulceration, reflecting a reparative process. Squamous atypia has been reported in 2 to 3 percent of all cervical smears (300,349).

The role of HPV in the genesis of this lesion is not entirely clear. It has been reported that between 10 and 20 percent of women with smears showing squamous atypia of a type associated with a reactive process have HPV DNA, as detected by nucleic acid hybridization tests

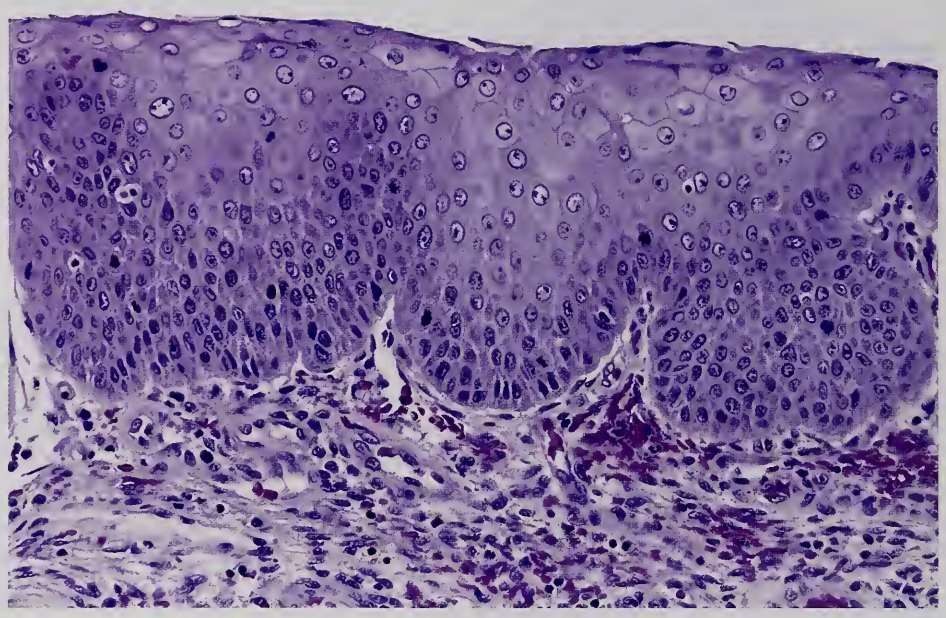


Figure 5-9

SQUAMOUS ATYPIA, REACTIVE TYPE

The squamous mucosa shows maturation but the basal zone is widened and contains several mitotic figures. Cells have enlarged vesicular nuclei with prominent nucleoli.

(246,354), similar to the frequency in normal controls. Squamous atypia may therefore encompass a heterogeneous group of lesions, most unrelated to HPV infection and some possibly representing the earliest, but nonspecific, cellular manifestations of HPV infection.

Microscopic Findings. The squamous epithelium may be glycogenated and may or may not be slightly thickened. The cellular organization and maturation are normal. There is little evidence of proliferation in the parabasal cell layer. Generally, there is minimal mitotic activity. Mitotic figures may be present as a reflection of repair, but are limited to the deeper layers of the epithelium (fig. 5-9). Immunohistochemical stains for Ki-67 confirm this finding since labeled cells are limited to the deeper layers. Abnormal mitotic figures are rarely seen. If present, the lesion should be considered a squamous intraepithelial lesion (SIL), most likely high-grade, until proven otherwise as it is likely that superimposed inflammation has altered the appearance of the underlying SIL.

The nuclei in reactive squamous atypia are enlarged and round. The nuclear chromatin is finely granular and nucleoli are prominent. The nuclear membranes may be smooth or only slightly irregular and lack significant wrinkling. Binucleate cells are occasionally present. The squamous cells have a normal nuclear-cytoplasmic ratio, and intercellular bridges are usually evident. Typically, there is an associated acute and chronic inflammatory infiltrate in the stroma, with leukocytes within the epithelium. The nuclei in squamous atypia that are thought to reflect possible HPV infection generally exhibit some of the features seen in LSIL but not to a sufficient degree to permit definitive diagnosis; however, determining the low end of the morphologic spectrum of LSIL is subjective and poorly reproducible.

Cytologic Findings. In cytologic preparations, the nuclear features that are thought to be related to reactive and reparative processes are the same as in tissue specimens, with nuclear enlargement, open vesicular chromatin, and evident nucleoli (fig. 5-10). Aggregates of squamous metaplastic cells exhibiting these nuclear features, accompanied by elongated cytoplasmic processes imparting a spindled/fibroblastic appearance, have been designated *atypical repair* (fig. 5-11). Atypia related to radiation therapy is characterized by nuclear enlargement accompanied by increased amounts of cytoplasm, resulting in a generally normal nuclear-cytoplasmic ratio (fig. 5-12). The nuclei are markedly enlarged and display vesicular chromatin with evident nucleoli; smudgy degenerative nuclear changes and air-drying artifact can be seen in cytologic smears.

Atypical squamous cells, possibly related to HPV infection, are divided into two types according to the Bethesda System for interpreting cytologic specimens (287). Superficial and intermediate cells exhibiting mild nuclear

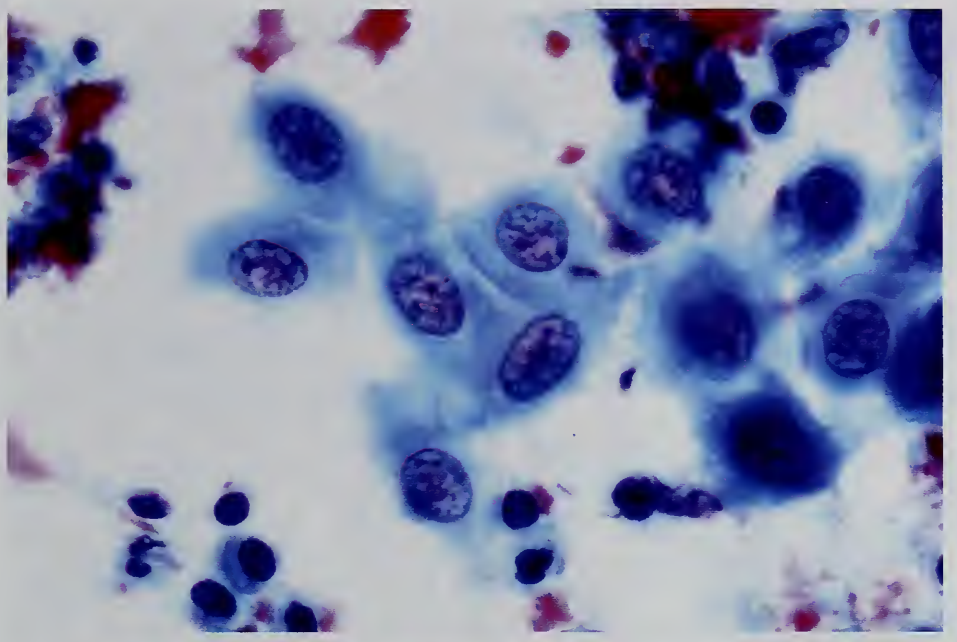


Figure 5-10

SQUAMOUS METAPLASIA WITH REACTIVE ATYPIA

The metaplastic squamous cells contain enlarged, vesicular nuclei with smooth membranes and evident nucleoli.

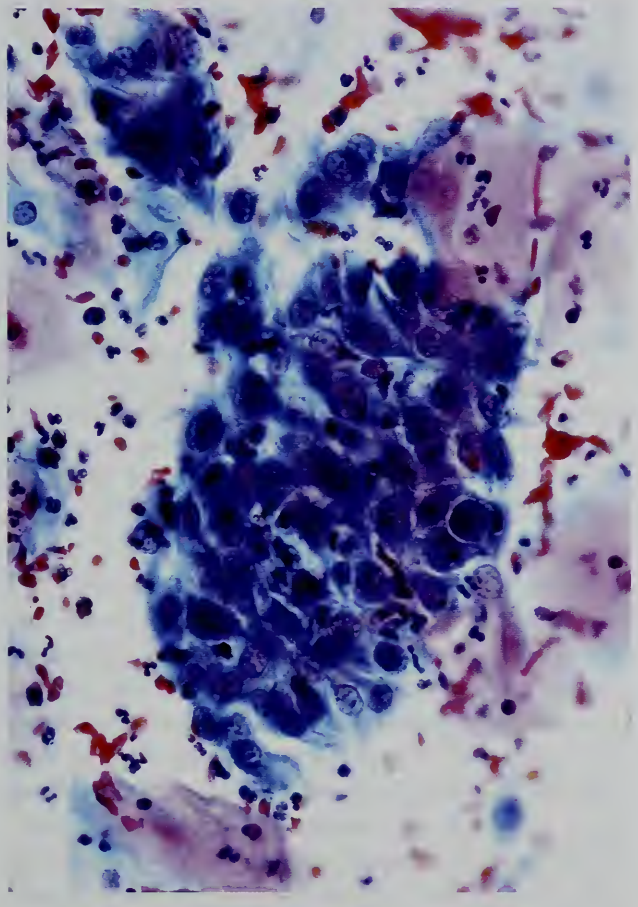


Figure 5-11

SQUAMOUS ATYPIA (ATYPICAL REPAIR)

Aggregates of squamous metaplastic cells have elongated cytoplasmic process and contain enlarged nuclei with prominent nucleoli.

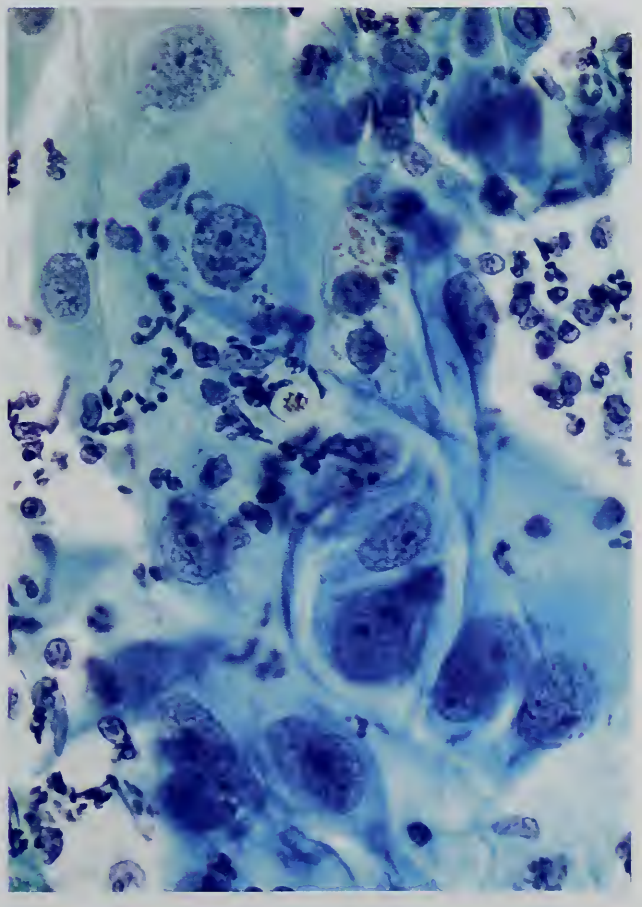


Figure 5-12

SQUAMOUS ATYPIA ASSOCIATED WITH RADIATION THERAPY

The squamous cells have markedly enlarged vesicular nuclei with prominent nucleoli. The cytoplasm is abundant and normal nuclear-cytoplasmic ratios are maintained.

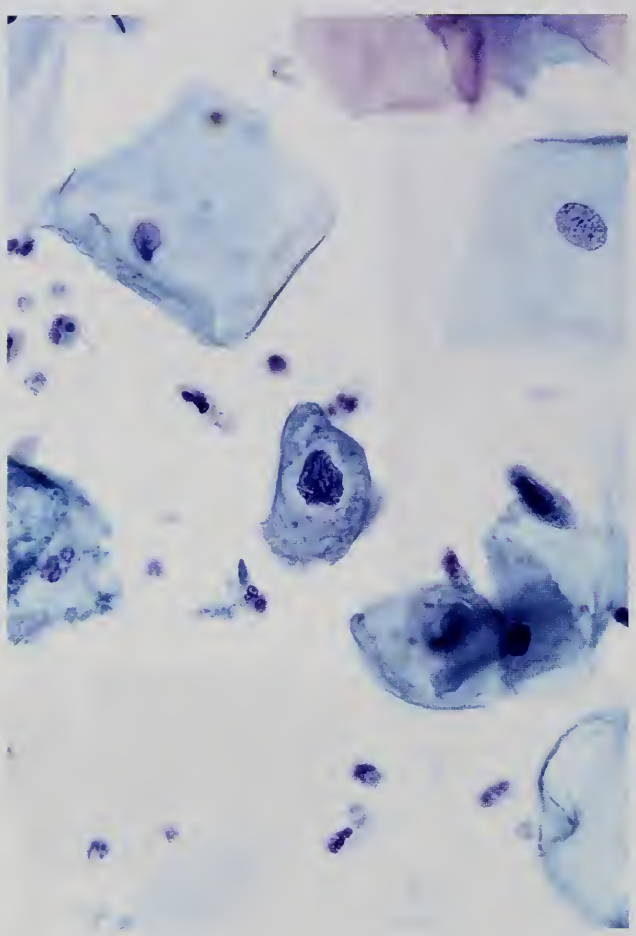


Figure 5-13

ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE (ASC-US)

A single atypical cell has a slightly enlarged nucleus with some hyperchromasia, an irregular nuclear membrane, and perinuclear cytoplasmic clearing. These findings are insufficient to diagnose low-grade squamous intraepithelial lesion (LSIL) but a positive HPV test for high-risk types supports interpretation as biologically equivalent to LSIL for management purposes.

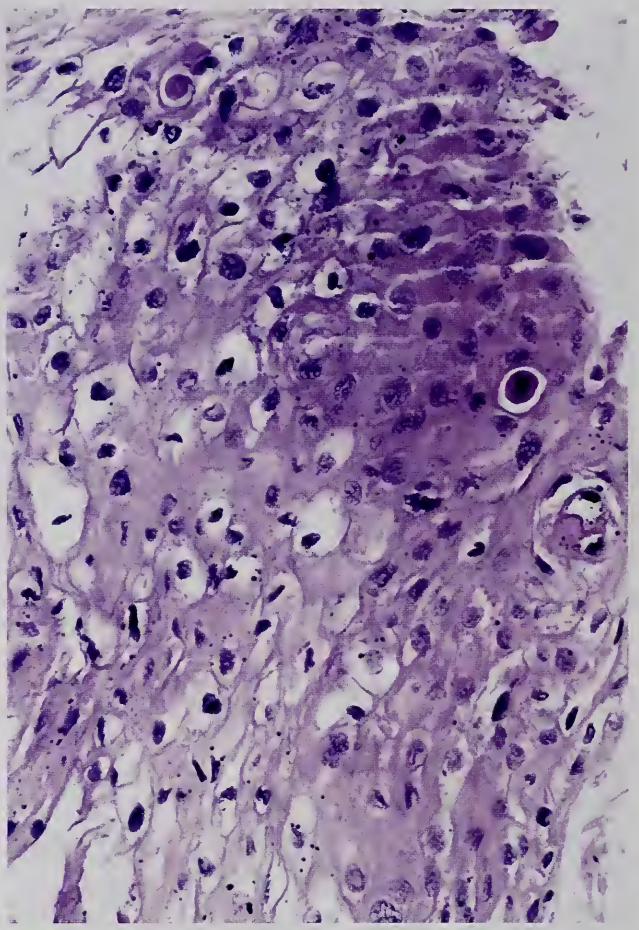


Figure 5-14

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION

A follow-up biopsy of the lesion seen in figure 5-13 shows a fragment of mature squamous epithelium exhibiting nuclear atypia, characterized by variably sized and shaped hyperchromatic nuclei with nuclear membrane irregularities, coupled with cytoplasmic clearing (koilocytosis).

enlargement and chromatin abnormalities insufficient for a diagnosis of LSIL are classified as ASC-US (figs. 5-13, 5-14). Metaplastic cells exhibiting nuclear abnormalities insufficient for a definitive diagnosis of HSIL are classified as atypical squamous metaplastic cells, cannot exclude HSIL (ASC-H). Small atypical cells with high nuclear-cytoplasmic ratios and hyperchromatic but degenerative nuclei simulating HSIL are also associated with the use of intrauterine contraceptive devices (fig. 5-15).

Differential Diagnosis. Squamous atypia should be distinguished from LSIL and HSIL and squamous carcinoma (see below). In LSIL, in contrast to squamous atypia, the cellular architecture is disorganized and maturation is abnormal. Usually, there is some degree of proliferation in the parabasal layer. The nuclear membrane is wrinkled and irregular in contour. The cell membrane is thickened, and the nucleus is often eccentric within the perinuclear clear zone. HSIL, in contrast to squamous atypia, shows high mitotic activity, including abnormal mitotic figures, and the nuclei show greater pleomorphism and hyperchromasia. There is marked cellular crowding and disorganization, with loss of normal squamous maturation.

Squamous atypia is often associated with endocervical glandular atypia, which is characterized by a single layer of epithelial cells

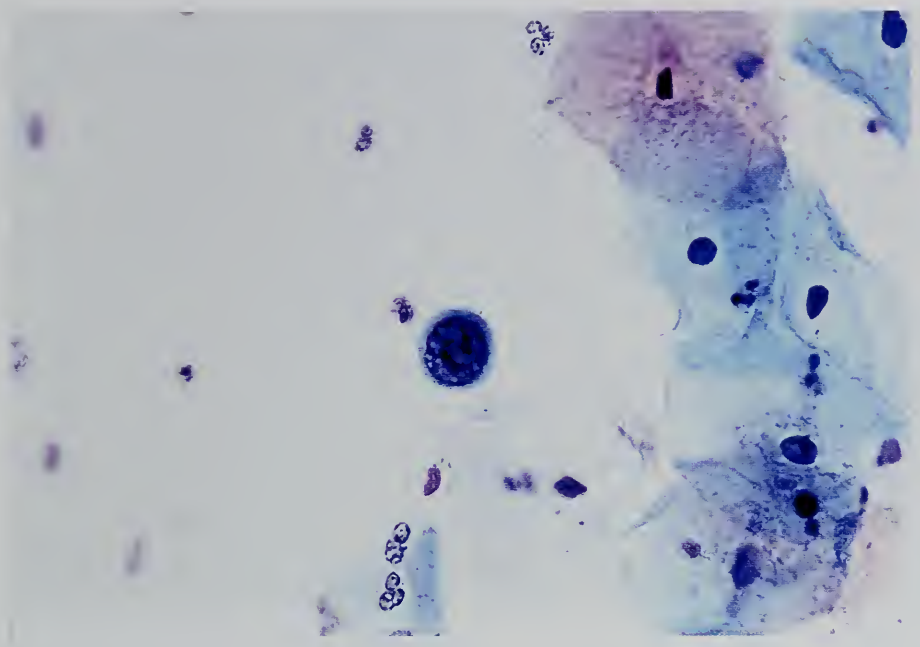


Figure 5-15

ATYPICAL SQUAMOUS CELL ASSOCIATED WITH INTRAUTERINE DEVICE USAGE

A single, small atypical cell has a high nuclear-cytoplasmic ratio and hyperchromatic nucleus, simulating HSIL, but the chromatin is degenerative appearing.

displaying similar abnormalities to those seen in the squamous epithelium. Squamous atypia is often related to inflammation and repair but sometimes there is no associated abnormality that explains the atypia.

Squamous Intraepithelial Lesions

Definition. Proliferative *squamous intraepithelial lesions* (SILs) display abnormal maturation, nuclear enlargement, and nuclear atypia, with the latter characterized by pleomorphism, coarse chromatin clumping, and irregular nuclear contours. SILs have been designated dysplasia (graded as mild, moderate, or severe) and cervical intraepithelial neoplasia (CIN, grades 1-3). In our routine practice, we apply the Bethesda System of terminology for cytologic classification to histologic specimens and have adopted that system for this Fascicle as well. Accordingly, flat lesions with mildly defective squamous maturation, accompanied most often by koilocytotic atypia and mitotic activity confined to the lower third of the epithelium, are classified as LSIL, which encompasses mild dysplasia, CIN 1, and koilocytotic atypia. Lesions exhibiting greater degrees of immaturity, accompanied by moderate to marked nuclear atypia and mitotic activity in the middle or upper thirds of the epithelium, are classified as HSIL, which encompasses moderate and severe dysplasia, CIN 2 and CIN 3, and carcinoma in situ (1,381). It is not necessary to report the presence of koilocytotic atypia in either low- or high-grade lesions. A more detailed discussion of terminology is presented in chapter 4.

General Features. SIL is predominantly a disease of women in the reproductive age group with the same risk factors as a sexually transmitted disease. The prevalence of SIL in different populations varies widely depending on the underlying risk factors in the population and the extent of cytologic screening. In the United States, the prevalence of SIL in women undergoing cytology screening based on surveys from the College of American Pathologists and the National Breast and Cervix Cancer Early Detection Program (NBCCEDP) ranges from 1.97 to 2.9 percent for LSIL to 0.5 to 0.8 percent for HSIL (185,235). Based on the data from the NBCCEDP, rates of cytologic and biopsy-confirmed LSIL and HSIL decrease with increasing patient age. Among women undergoing screening at Kaiser Permanente in Northern California, the frequency of biopsy-confirmed HSIL was reported to be 92 percent in women under 40 years and 21 percent in women over 40 (213). Only 5 percent of HSIL occurred in women under 20 years, whereas approximately 80 percent of HSIL was detected in women 20 to 40 years of age. In contrast, the rate of biopsy-confirmed invasive cervical cancer increased until 64 years of age. The mean age of women with SIL in one large study was 26 years (345), approximately 20 years younger than that of women with invasive carcinoma.

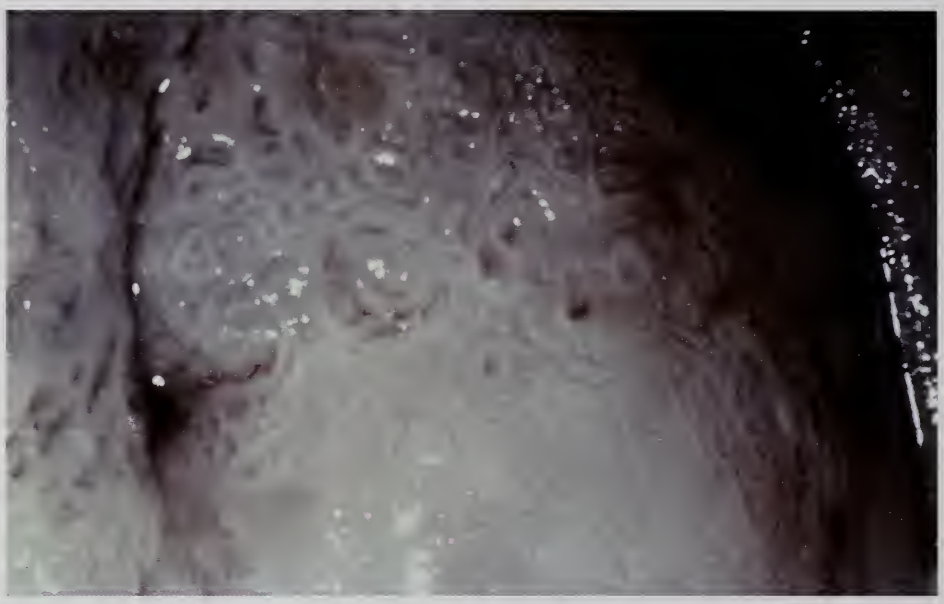


Figure 5-16

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION

Colposcopic view reveals acetowhite epithelium involving the ectocervical mucosa and transformation zone.

With the introduction of mass cytology screening programs, the prevalence of invasive carcinoma has decreased dramatically, whereas that of the precursor lesions has risen (65). Over the past few decades, SIL has become increasingly common and is being detected in increasingly younger women, including teenagers. Cytologic evidence of HSIL can now be found in women under the age of 15 years, and the age-specific incidence for CIN 3 currently peaks in the 25- to 29-year-old group (353). The prevalence of SIL in the 15- to 19-year age groups has been reported to be as high as 18.8/1,000 (345). These epidemiologic changes have been attributed to changes in sexual behavior.

The precursor lesions of cervical cancer have many of the same risk factors as invasive carcinoma. The major independent risk factors in recent case-control studies of cervical cancer precursor lesions are HPV infection, lifetime number of sexual partners, and a history of cigarette smoking (355). The view that cervical cancer and SIL are sexually transmitted diseases is substantiated by studies linking a woman's risk of developing cervical cancer with the sexual behavior of her sexual partner. For example, it has been shown that there is a strong correlation between the average number of sexual partners of men and the incidence of cervical cancer in their spouses who were allegedly monogamous (46).

Other factors such as coital frequency, menstrual patterns, parity, and number of children are covariables. The relative risk of cervical cancer increases with duration of oral contraceptive use. This finding is similar for all women when adjusted for HPV status, sexual partners, previous cervical smears, smoking, and use of barrier methods of contraception, and applies to invasive and in situ squamous carcinoma and adenocarcinoma of the cervix (380). It is now well established that high-risk HPVs are the major causal factor for the development of HSIL and cervical cancer. This is discussed in detail in chapter 3.

Gross Findings. The gross appearance of SIL is best appreciated by colposcopic examination of the transformation zone after application of 3 to 5 percent acetic acid. A variety of colposcopic patterns, including white epithelium, punctation, and "mosaicism," reflect the histologic changes in the epithelium and underlying vasculature (figs. 5-16, 5-22). These colposcopic patterns occur in squamous metaplasia, cervicitis, and SIL. With experience, a rough correlation between the colposcopic appearance and the grade of the SIL can be made.

The boundary of intraepithelial lesions is limited by their border with the native squamous epithelium of the ectocervix, but proximally, the lesion can extend for a variable distance into the endocervical canal, and rarely even into the endometrium, fallopian tube, and peritoneal surfaces. SIL occurs twice as often on the anterior lip of the cervix as on the posterior lip; it does not usually involve the lateral portions of the transformation zone.

Microscopic Findings. SIL is characterized by abnormal cellular proliferation and maturation, and nuclear atypia. The proliferation begins in the basal and parabasal layers, with an increase in the number of immature parabasal cells, which extend to a variable degree into the intermediate and superficial layers. Mitotic activity is typically increased. Although abnormal mitotic figures are occasionally identified in low-grade lesions, they are found with increasing frequency in high-grade lesions. Abnormal mitotic figures display a variety of configurations, including two-group metaphase, three-group metaphase, ring mitosis, V-shaped metaphase, tripolar mitosis, dispersed metaphase, giant mitosis, and other bizarre forms (119). Although dispersed metaphase and tripolar mitotic figures may occur in diploid or polypoid lesions, the other abnormal forms are usually associated with aneuploidy.

Abnormal maturation, manifested by loss of polarity and cellular disorganization, is an important feature of SIL. The degree of maturation is inversely related to the severity of the lesion. Immature parabasal cells have a high nuclear-cytoplasmic ratio. As maturation occurs in the more superficial layers, these cells acquire more eosinophilic cytoplasm. Low-grade lesions show a greater degree of maturation on both an individual cell basis and the extent to which the upper levels of the epithelium contain cells with abundant cytoplasm. Despite undergoing maturation, the cells on the surface still contain abnormal nuclei, which permit their detection in cytologic smears.

Nuclear atypia is the hallmark of SIL, and it takes two forms that often overlap, making distinction on a cell-by-cell basis sometimes difficult or impossible. One form, occurring mainly in the superficial levels, is a manifestation of productive HPV infection. It often occurs in the koilocytes (see below). The other form resembles that seen in malignant tumors. Cells displaying this type of atypia are present in the deep layers of the epithelium and occupy progressively more of the epithelium in high-grade lesions. This type of nuclear atypia is characterized by an increased nuclear-cytoplasmic ratio, coarse chromatin, an increased number of chromocenters, hyperchromasia, irregular nuclear membranes, and pleomorphism.

Koilocytosis, or *koilocytotic atypia*, is a common feature of SIL and, when strictly defined, is indicative of the cytopathologic effect of HPV on squamous epithelium in the lower female genital tract. Most examples of koilocytosis are correlated with productive HPV infection, however, rarely koilocytosis is found in higher-grade lesions including invasive squamous cell carcinoma. In the latter case, it is usually not correlated with the presence of virions. Koilocytosis, therefore, should not be considered evidence of a benign viral lesion. Conversely, not all HPV-related lesions exhibit koilocytosis; adenocarcinoma of the cervix lacks this feature, as do many HSILs and squamous carcinomas. Also, virions, capsid antigen, and HPV DNA are not always detectable in cells resembling koilocytes within or outside the lower female genital tract (personal observations). For example, the squamous component of endometrioid carcinoma of the endometrium or ovary may exhibit cytoplasmic vacuolization and nuclear atypia closely resembling koilocytosis, but HPV DNA is not detected in these tumors.

The mature intermediate or superficial cell that displays koilocytosis has two characteristic features: 1) a clear, sharply defined perinuclear cavity associated with a peripheral rim of thickened cytoplasm, and 2) nuclear atypia (figs. 5-17–5-21) (225). Nuclear atypia is characterized by enlargement, hyperchromasia, and coarsening of the chromatin. The chromatin is often dispersed along the nuclear membrane, which appears thickened and irregular. The nucleus may be central and round but more often is displaced to the periphery of the cell. Most of the cytoplasm is clear (referred to as cavitation) and the cellular membrane appears thickened. Ultrastructural studies have shown perinuclear cytoplasmic necrosis, with the cytoplasmic fibrils condensed along the periphery of the cell (224); viral particles are present in crystalline array within the nucleus.

Besides koilocytosis, there are other less specific cytologic manifestations of HPV infection. Cells near the surface in which HPV structural protein and DNA have been identified have rounded, flattened, or raisin-shaped pyknotic nuclei and inconspicuous or absent cytoplasmic clearing (230). The nuclear-cytoplasmic ratio of these cells is typically increased, and nuclear pleomorphism may be marked. Mononucleate or multinucleate, highly pleomorphic bizarre cells

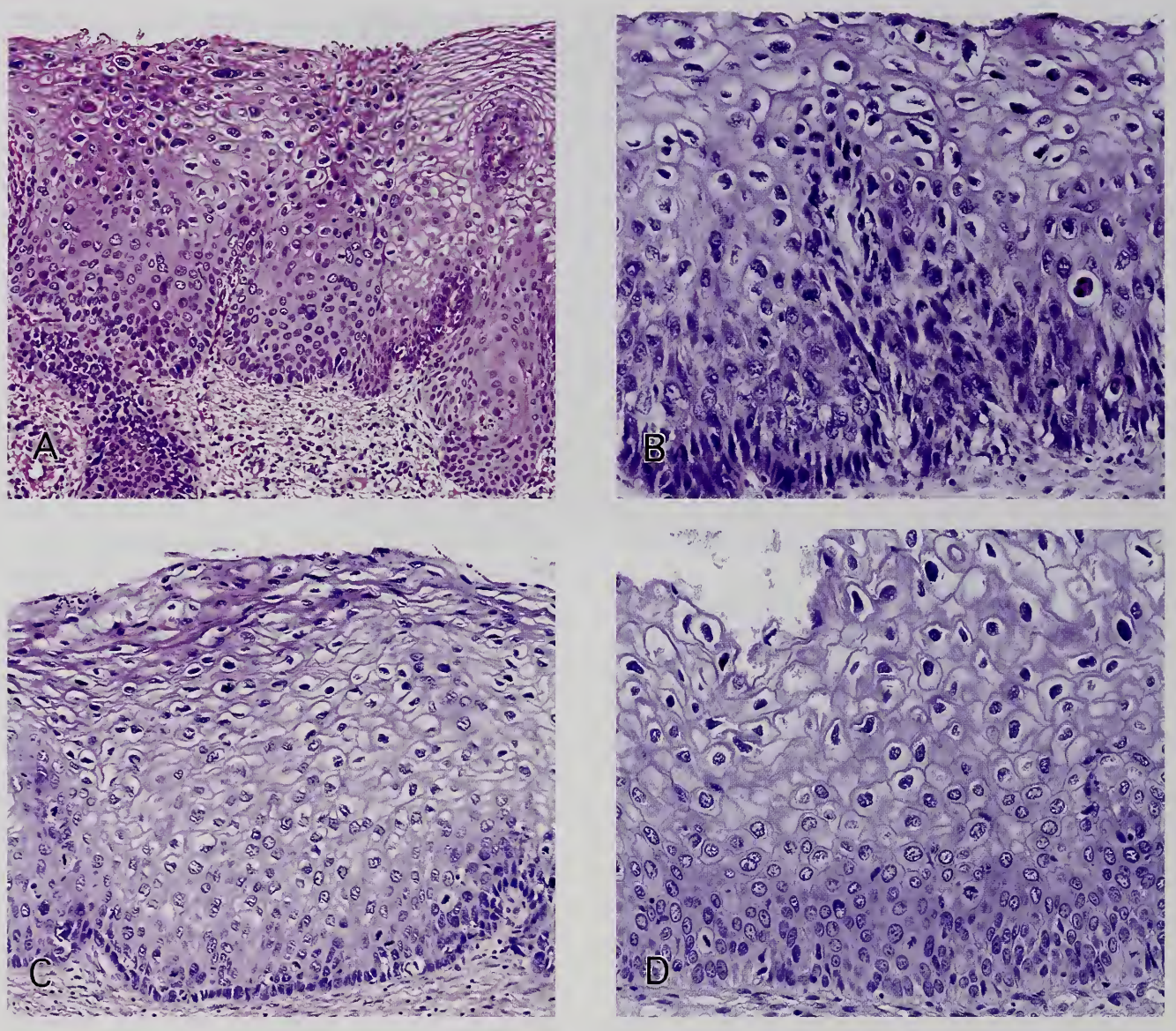


Figure 5-17

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION

A: Compared with normal mature squamous epithelium (right), lesional epithelium exhibits parabasal zone widening, mitotic figures in the lower third of the epithelium, and nuclear abnormalities in intermediate and superficial cells, characterized by nuclear enlargement, hyperchromasia, and irregular nuclear membranes.

B: The lesional epithelium exhibits parabasal zone widening, mitotic figures in the lower third of the epithelium, and nuclear abnormalities accompanied by cytoplasmic clearing (koilocytosis).

C: Squamous epithelium shows cytoplasmic maturation but the nuclei are abnormal, characterized by enlargement and hyperchromasia in the middle and upper layers. This nuclear abnormality is accompanied by prominent cytoplasmic clearing (koilocytosis).

D: The parabasal zone is widened, with several mitotic figures evident but confined to the lower third of the epithelium. HPV-related cytopathic effect (koilocytosis) is present, characterized by mild nuclear enlargement and hyperchromasia accompanied by cytoplasmic clearing.

are commonly observed in the superficial layers (226,268,326). Cells near the surface may have nuclei that are smaller and pyknotic. Nuclei that are hyperchromatic have smudged chromatin, probably reflecting a degenerative change.

Koilocytosis may be confused with normal squamous epithelium with prominent cytoplasmic vacuolization due to the presence of glycogen. Indeed, in studies in which cervical biopsies interpreted by community pathologists

were evaluated by an expert panel of gynecologic pathologists, nearly half of LSIL/CIN 1/koilocytotic atypia cases classified by the community pathologists were interpreted as negative by the panel. The consensus panel diagnoses correlated highly with the presence of HPV DNA (390). Koilocytosis is often a discrete focal lesion, whereas the vacuolated cells in normal epithelium occupy a large ill-defined area.

Microscopic Grading. SIL is composed of a heterogeneous population of cells displaying wide diversity in the degree of maturation, proliferation, and atypia (315,332). As indicated in chapter 4, we advocate the use of a binary grading system comparable to the Bethesda System used for cytologic interpretation to subdivide SIL into LSIL and HSIL.

Squamous intraepithelial lesions have been traditionally graded according to the extent of replacement of the epithelium by abnormal proliferating parabasal cells. With the binary grading system, however, greater emphasis is placed on cytologic atypia and mitotic activity, including the presence of abnormal mitotic figures.

Low-Grade Squamous Intraepithelial Lesion (LSIL). Proliferating parabasal cells occupy the lower third of the epithelium. Although the upper two thirds of the epithelium contain mature cells, they are abnormal. Cells with enlarged pleomorphic nuclei with hyperchromatic, often smudged chromatin may be present but these are degenerated cells resulting from productive viral infection (figs. 5-17, 5-18). Despite the presence of these atypical cells in the upper levels of the epithelium, this should not be interpreted as full-thickness replacement of the epithelium by abnormal proliferating parabasal cells. The abnormal cells of LSIL that are present in the upper levels of the epithelium have abundant cytoplasm and lack mitotic activity. In contrast, abnormal proliferating parabasal cells, which do extend into the middle and upper levels of the epithelium and characterize HSIL, have a high nuclear-cytoplasmic ratio and nearly always evident mitotic activity.

The hallmark of LSIL is koilocytosis, which is generally most evident in the upper levels of the epithelium overlying the proliferating parabasal cells in the deeper levels (lower third) (figs. 5-17–5-22). Also included in this category are koilocytotic lesions with minimal or no evidence of proliferation in the parabasal layer, termed "flat condyloma" in the past (a term that should not be used for these lesions). Lesions classified as LSIL display a wide morphologic range. Almost all show some degree of koilocytotic atypia. The nuclear atypia in LSIL reflects the changes associated with productive viral infection. These changes include nuclear gigantism, probably a result of polyploidy, multinucleation, coarse chromatin, and irregular nuclear membranes. Most important, particularly in distinguishing LSIL from highly glycogenated metaplastic squamous epithelium, there is cellular disarray, which may be present at all levels of the epithelium, and a lack of orderly maturation as cells approach the surface. This feature is particularly useful in lesions with less-developed koilocytosis. In these lesions, instead of nuclei becoming progressively smaller as they approach the surface, they retain the size of nuclei in the deeper levels. Mitotic figures are generally present but usually to a much lesser degree than in high-grade lesions. They are nearly always located in the lower levels but occasionally extend nearly halfway up the epithelium. Mitotic figures near the surface are unusual in LSIL and abnormal mitotic figures are distinctly unusual; these features indicate the lesion is more likely HSIL. In all forms of SIL, nucleoli are usually not visible or are indistinct.

High-Grade Squamous Intraepithelial Lesion (HSIL). When the proliferation of atypical parabasal cells involves greater than one third of the thickness of the epithelium, the lesion is classified as HSIL. Koilocytosis may occur in HSIL but does so less often than in LSIL (fig. 5-23). The diagnosis of HSIL is based on the appearance of the nucleus and the extent of abnormal cellular maturation. Typically, HSIL is composed of immature parabasal cells with oval, round, or spindle-shaped nuclei oriented in a vertical fashion. The nuclear-cytoplasmic ratio is high; cells are crowded and overlap, and are haphazardly distributed. The nuclear membranes are irregular and notched. The abnormal cells extend into the middle and upper layers of the squamous epithelium. Occasionally, there is discordance between the degree of maturation and the degree of nuclear atypia in HSIL. This type of HSIL has been referred to as *metaplastic dysplasia* or *eosinophilic dysplasia* (figs. 5-24, 5-25) (311). It is characterized by cells with relatively

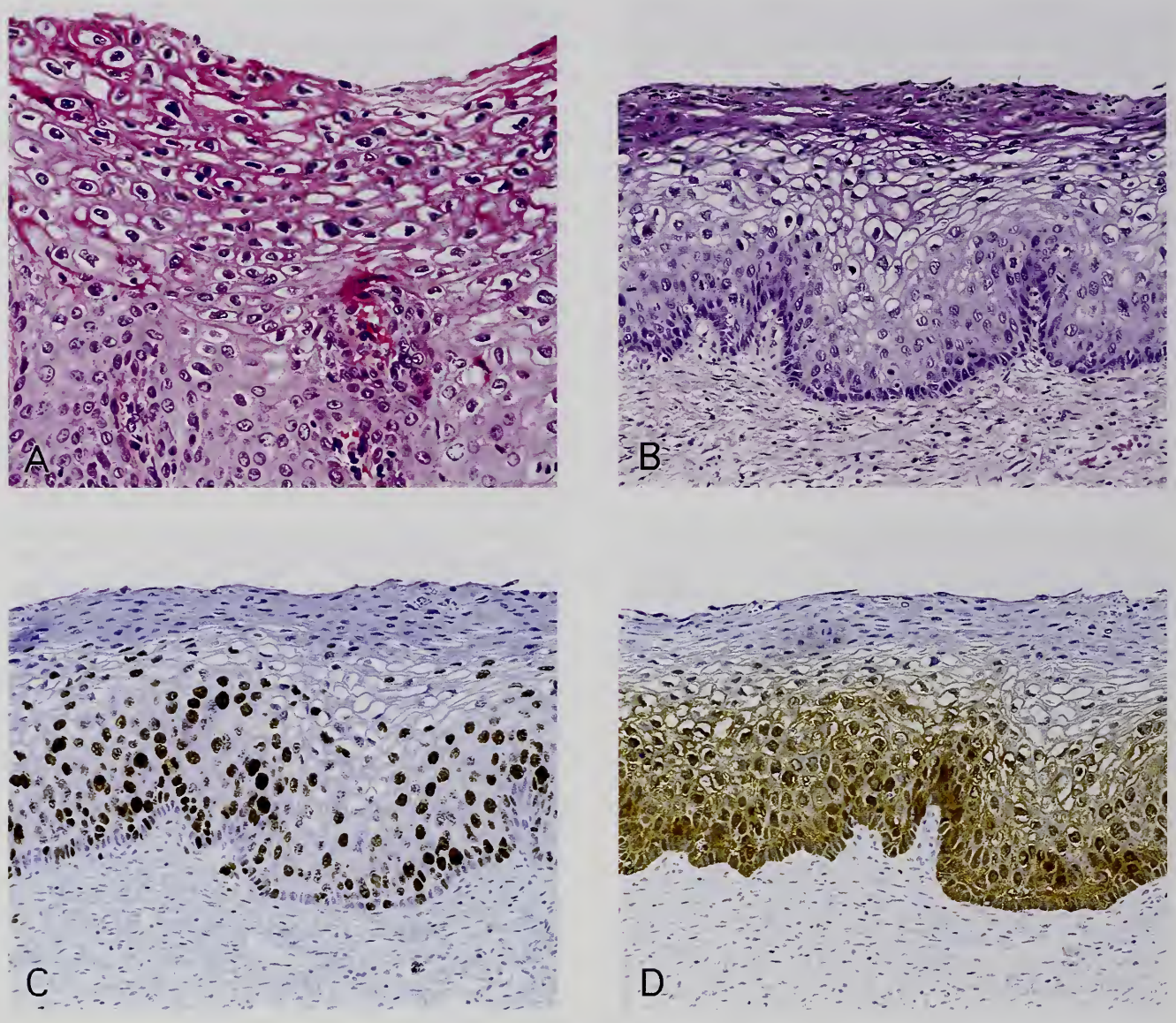


Figure 5-18

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION

A: HPV-related cytopathic effect (koilocytosis) is present in intermediate and superficial cells, and characterized by nuclear enlargement and hyperchromasia accompanied by cytoplasmic clearing.

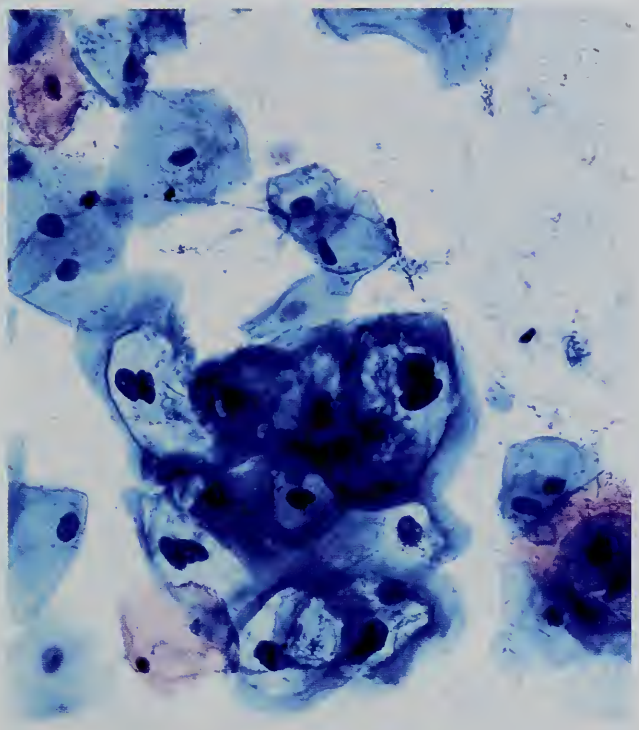
B: The parabasal zone contains mitotic figures. Cells in the intermediate and superficial layers have koilocytotic atypia.

C: The proliferation index, as assessed by immunohistochemical expression of Ki-67, is increased, with positive nuclei distributed in the parabasal and intermediate layers (deeper section of lesion in B).

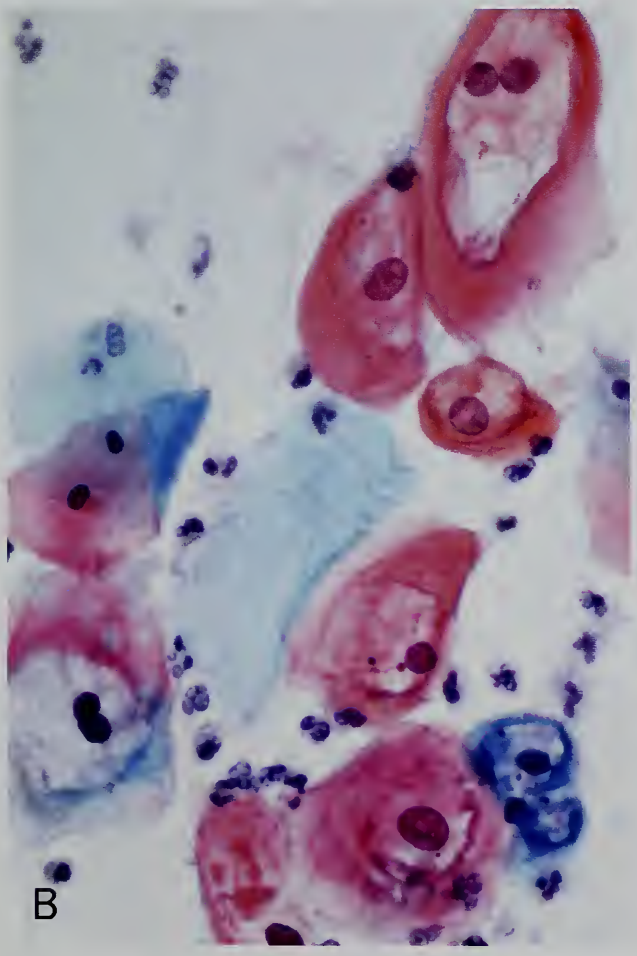
D: Diffuse expression of p16 in the lower half of the epithelium is characteristic of high-risk HPV-related LSIL (deeper section of lesion in B).

abundant eosinophilic cytoplasm and well-defined cell membranes containing atypical nuclei that are hyperchromatic and pleomorphic or uniform and vesicular, with coarse chromatin. The nuclear atypia is not of the characteristic type associated with productive HPV infection. The presence of mitotic figures in the middle third of the epithelium or significant nuclear atypia in the lower third assists in classifying these lesions as HSIL (figs. 5-26–5-30). Lesions in which only the lower third of the epithelium is replaced by proliferating parabasal cells but exhibiting marked nuclear atypia should be classified as HSIL.

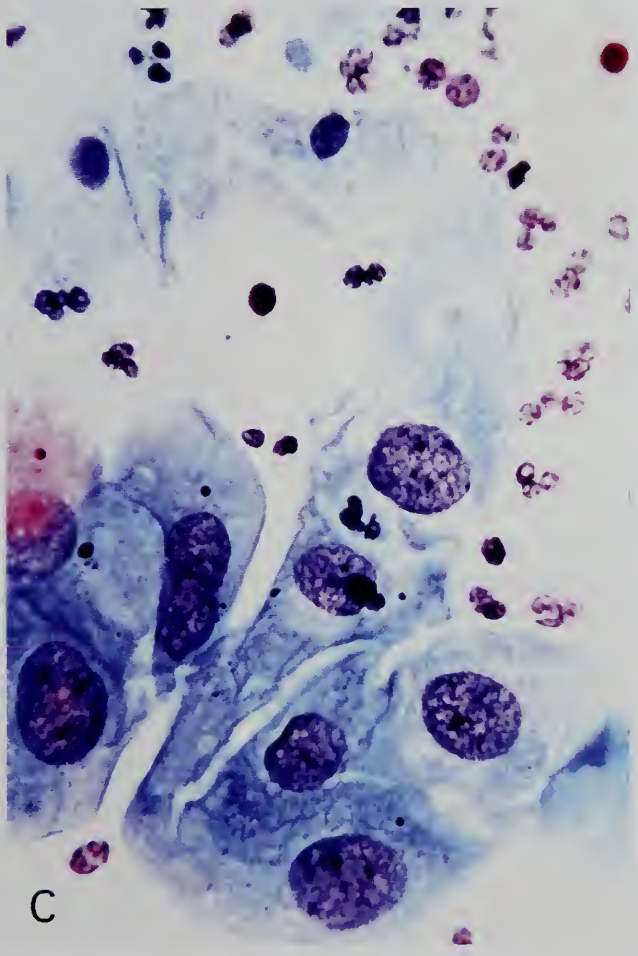
Typically, the epithelium of HSIL is composed of multiple layers of cells but occasionally lesions



A



B



C

Figure 5-19

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION

A,B: The cytologic preparation contains koilocytes, which are characterized by nuclear enlargement, hyperchromasia, binucleation, cytoplasmic clearing, and thick cytoplasmic rims.

C: These are intermediate type cells with nuclear enlargement and granular hyperchromasia. The abundant cytoplasm lacks clearing and thus classic koilocytosis is absent.

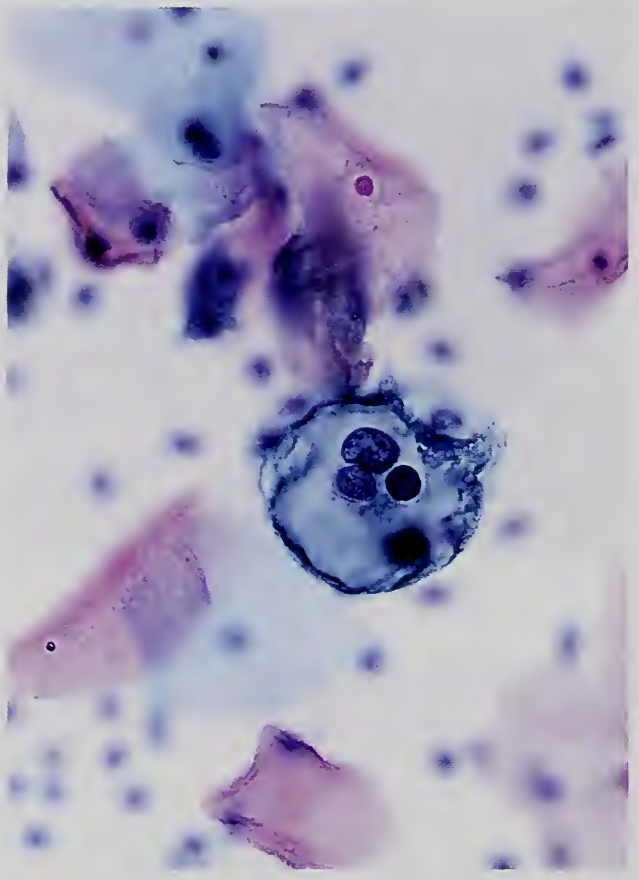


Figure 5-20

ATYPICAL SQUAMOUS CELL OF UNDETERMINED SIGNIFICANCE

A single atypical cell with mild nuclear enlargement, multinucleation, and cytoplasmic clearing is highly suggestive of LSIL, particularly in view of a positive high-risk HPV test result.

are only three or four cell layers thick. Often, HSIL extends into endocervical glands/crypts and undermines the preexisting endocervical glandular epithelium (fig. 5-31). When gland involvement is extensive, distinguishing HSIL from microinvasive squamous cell carcinoma can be difficult; the presence of rounded glandular contours distinguishes endocervical glands involved by HSIL from the irregular, paradoxically mature nests of microinvasive squamous carcinoma cells (fig. 5-31) (see Microinvasive Squamous Cell Carcinoma).

Sometimes HSILs are composed of cells with bland immature nuclei and inconspicuous or absent mitotic figures, suggesting the possibility of immature or atypical immature metaplasia. Evidence of almost any degree of mitotic activity, atypical mitotic figures, or any degree of cellular disarray should lead to the diagnosis of HSIL (figs. 5-32–5-34). A diagnosis of atypical immature metaplasia should be reserved for those lesions lacking the diagnostic features of HSIL that cannot be further classified as either negative or HSIL with ancillary techniques. Immunohistochemical assessment of the Ki-67 proliferation index and p16 expression is useful in this regard (see Immunohistochemical Findings).

At times it is difficult to classify a lesion as low or high grade. Careful assessment of the nuclear features, degree of maturation, and level of mitotic figures, combined with the assessment of additional levels, generally permits

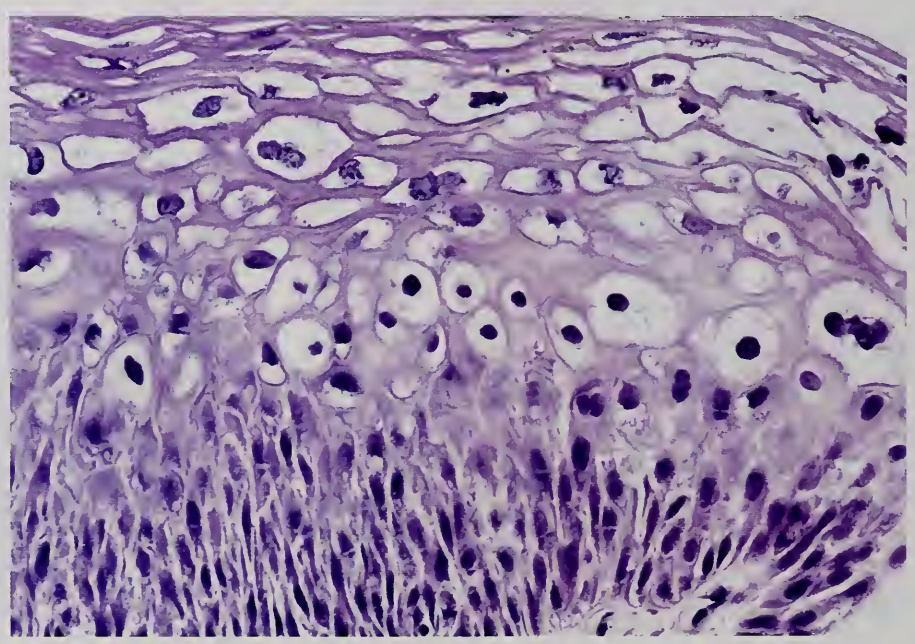


Figure 5-21

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION

A follow-up biopsy of the lesion seen in figure 5-20 demonstrates koilocytosis consistent with LSIL.

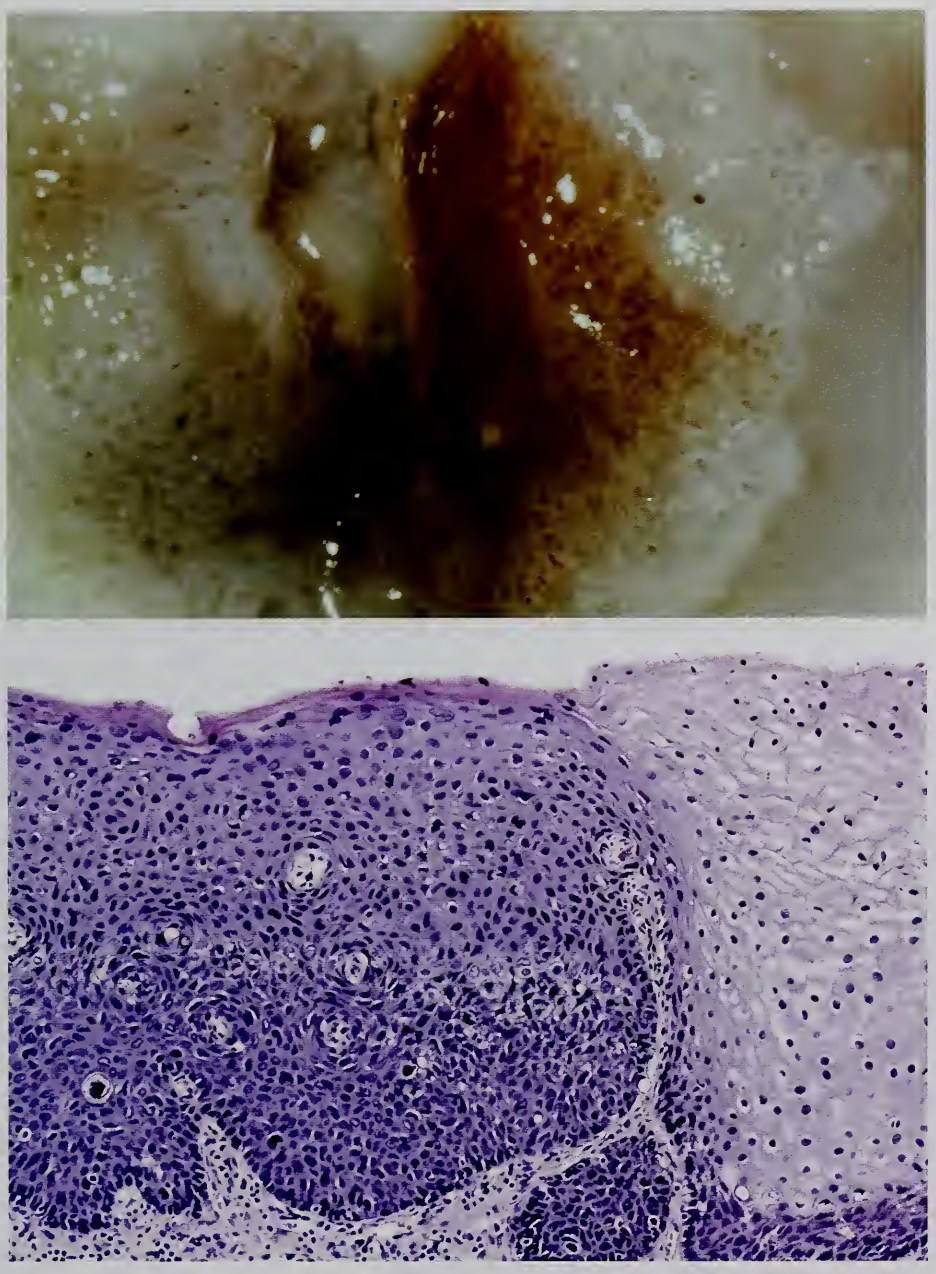


Figure 5-22

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION

Top: Colposcopic view reveals acetowhite epithelium with abnormal vascular patterns (punctation and mosaicism).

Bottom: Full-thickness proliferation of immature, atypical parabasal cells is evident adjacent to normal mature squamous epithelium, which shows early involvement of the parabasal zone.

classification as LSIL or HSIL. HSIL in excisional specimens obtained following the application of Lugol solution to the transformation zone for visualization of the lesion often exhibit an artifact characterized by a longitudinally demarcated eosinophilic zone in the upper portion of the lesion in which the epithelium appears more keratinized and mature, making grading difficult (fig. 5-35).

Cytologic Findings. LSIL is characterized by nuclear abnormalities and cytoplasmic changes in mature squamous cells having abundant well-defined cytoplasm. The cytologic features include nuclear enlargement (more than three times the size of a normal intermediate cell nucleus), which results in a slightly increased nuclear-cytoplasmic ratio; nuclear hyperchromasia with coarsely granular, smudged, or opaque chromatin; variation in nuclear size and shape; irregular nuclear membrane contours; and perinuclear cytoplasmic clearing or cavitation (koilocytosis) with a peripheral rim of dense cytoplasm (see figs. 5-19, 5-20) (287).

HSIL is characterized by cytologic changes occurring in cells that are smaller and more immature than those encountered in LSILs, generally the size of metaplastic and parabasal cells. Abnormal cells occur singly, in sheets, or in

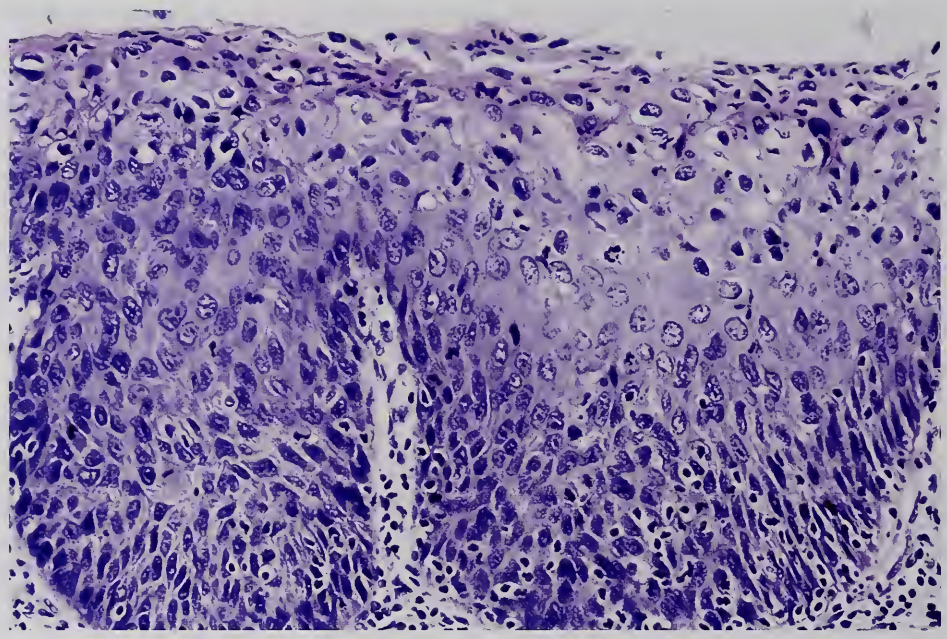


Figure 5-23

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE 2 [CIN 2])

The upper layers exhibit koilocytotic atypia, suggesting LSIL, but the extent of atypical parabasal proliferation and level of mitotic figures are sufficient to classify the lesion as HSIL.

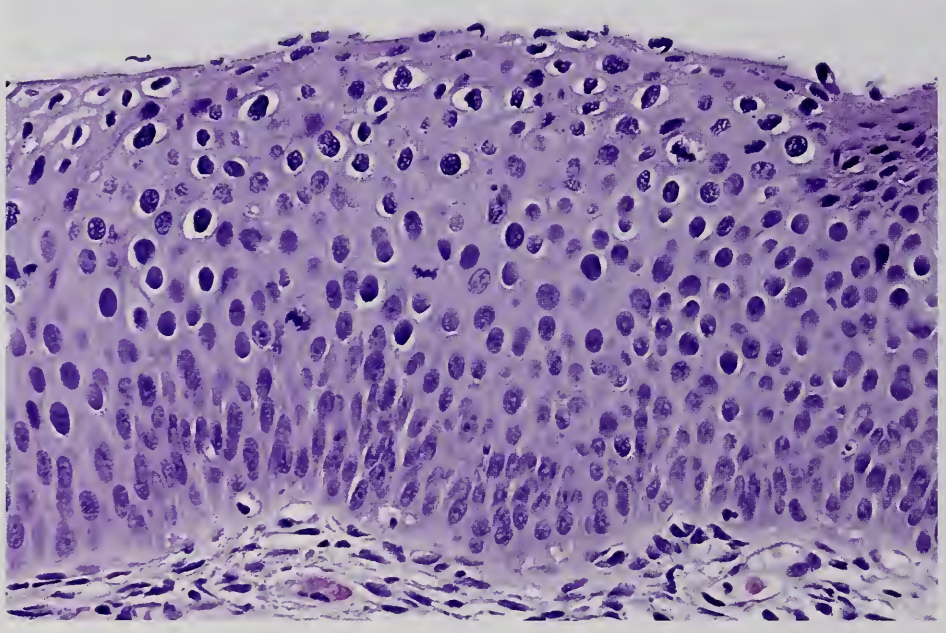


Figure 5-24

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CIN 2, METAPLASTIC TYPE)

Cells retain moderate amounts of eosinophilic cytoplasm but atypical parabasal cells and mitotic figures in the middle third qualify the lesion as HSIL.

syncytial aggregates. The degree of nuclear enlargement is variable but the cytoplasmic area is notably reduced, resulting in a much greater nuclear-cytoplasmic ratio than in LSIL. Nuclear membrane irregularities are present and chromatin is fine or coarsely granular and often hyperchromatic (this latter feature may be diminished or absent in liquid-based preparations). The cytoplasm may appear delicate, densely metaplastic, or even densely keratinized (figs. 5-36–5-39) (287).

HSIL with endocervical gland involvement is characterized by syncytial fragments of atypical immature parabasal type cells. These may have more delicate, vacuolated cytoplasm and form cellular aggregates displaying additional features suggestive of glandular differentiation, leading to interpretation as atypical glandular cells (fig. 5-40). The presence of such cells favors a diagnosis of neoplasia or adenocarcinoma in situ rather than HSIL. The presence of markedly atypical keratinized cells often suggests invasive squamous carcinoma but such cells can be exfoliated or obtained from the surface of a keratinizing HSIL involving the surface squamous mucosa or endocervical glands of the transformation zone (fig. 5-41).

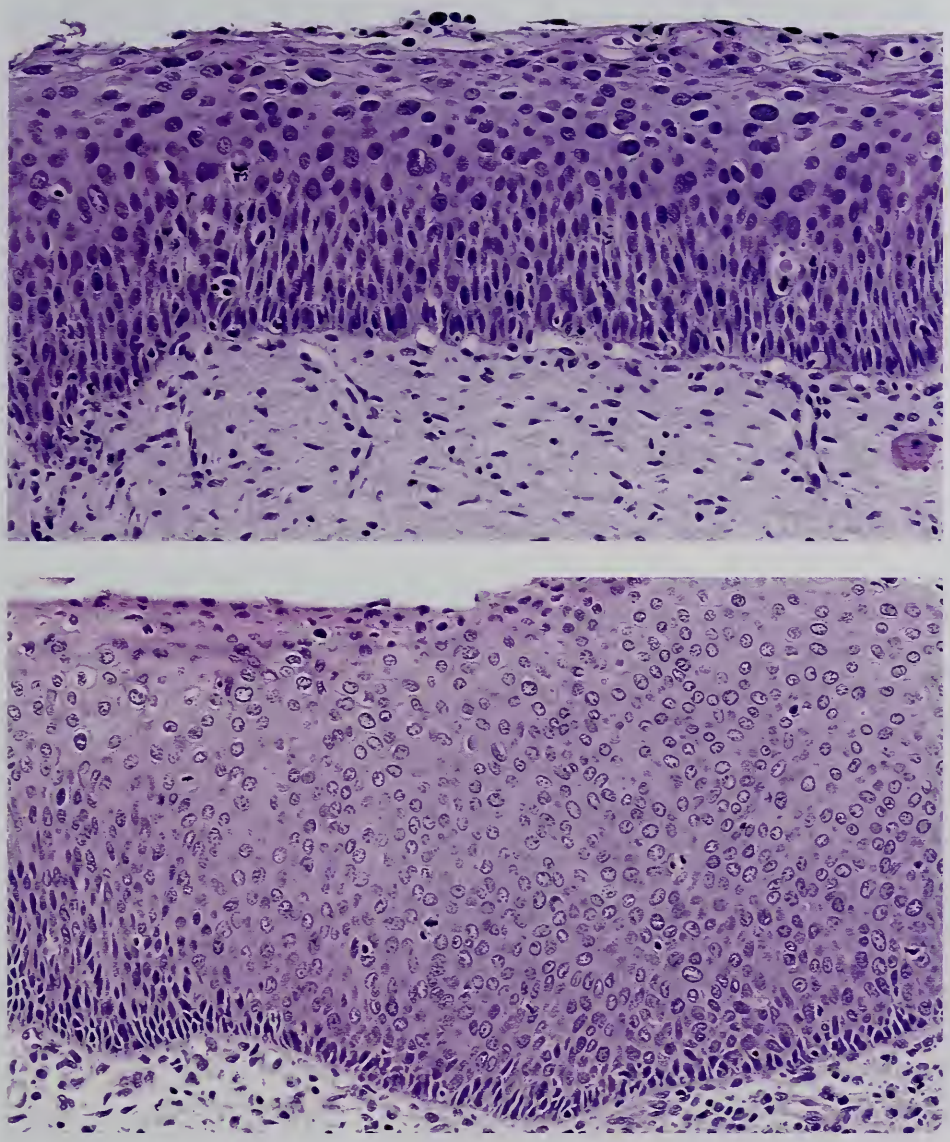


Figure 5-25

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CIN 2, METAPLASTIC TYPE)

Top: The cells retain moderate amounts of eosinophilic cytoplasm but atypical parabasal cells and a mitotic figure extending into the middle portion of the epithelium qualify the lesion as HSIL.

Bottom: Cells retain moderate amounts of eosinophilic cytoplasm and most have vesicular chromatin, but atypical parabasal cells fill the middle and upper thirds of the epithelium and a mitotic figure is evident in the middle of the epithelium, qualifying the lesion as HSIL.

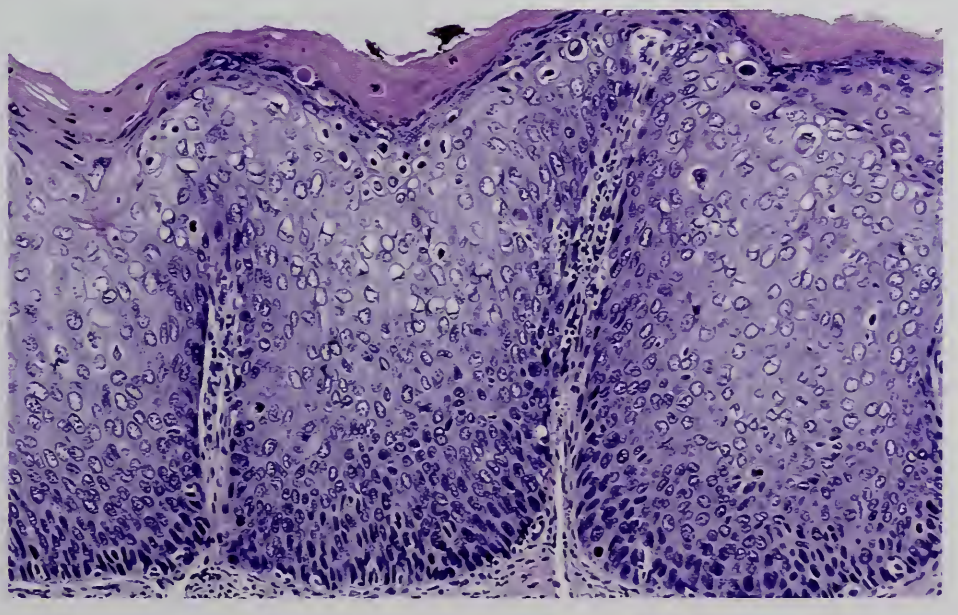


Figure 5-26

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CIN 2-3, KERATINIZING TYPE)

Atypical parabasal cells in the middle and upper thirds of the epithelium qualify the lesion as HSIL and the hyperkeratotic surface with an evident granular layer indicates a "keratinizing dysplasia."

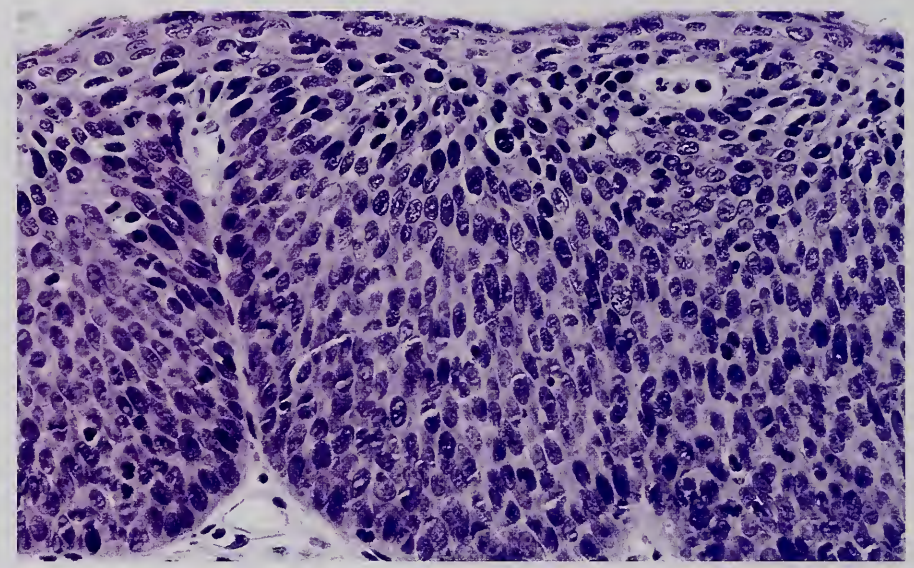


Figure 5-27

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CIN 3)

Full-thickness proliferation of atypical parabasal cells is characterized by marked nuclear enlargement and hyperchromasia.

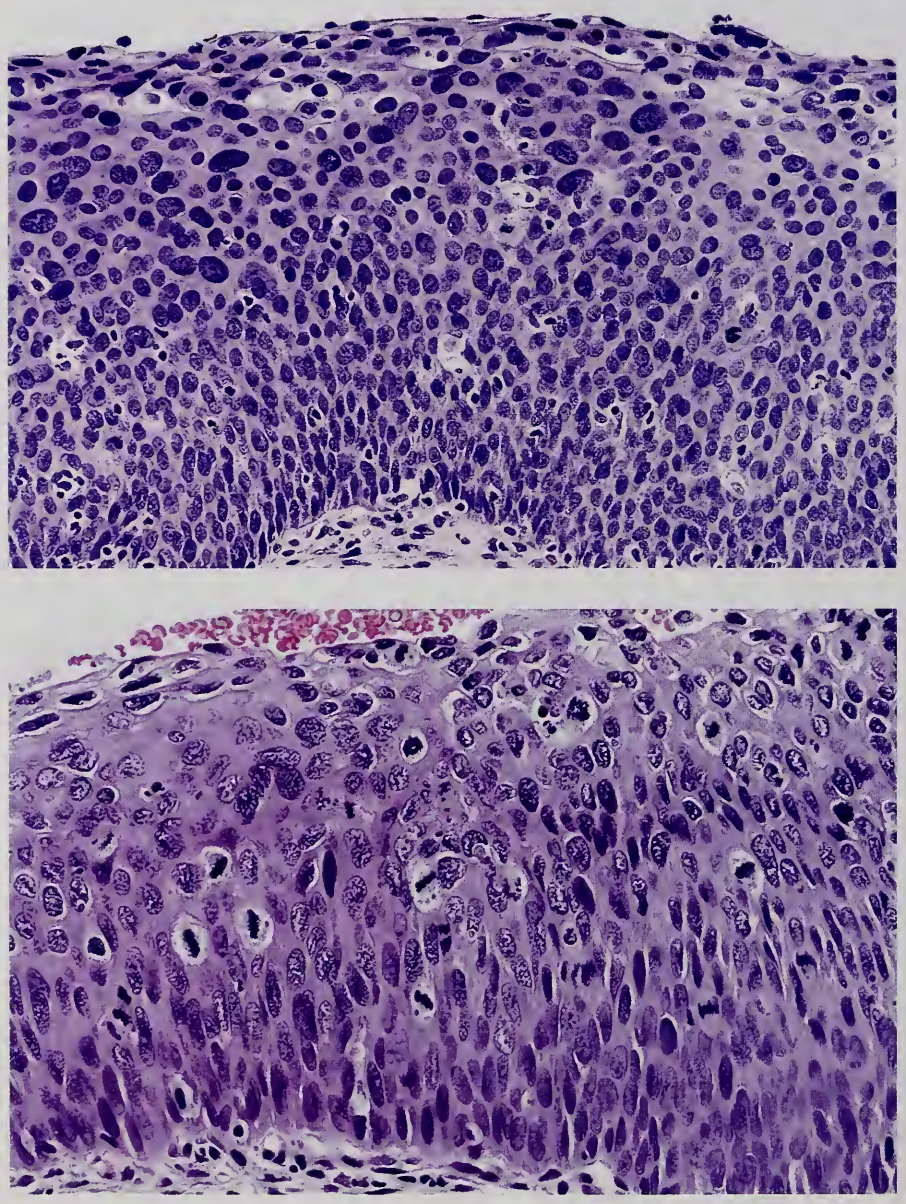


Figure 5-28

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CIN 3)

Top: Full-thickness atypical parabasal cell proliferation consists of disarrayed cells containing pleomorphic hyperchromatic nuclei.

Bottom: Numerous mitotic figures are evident at all levels of the atypical epithelium.

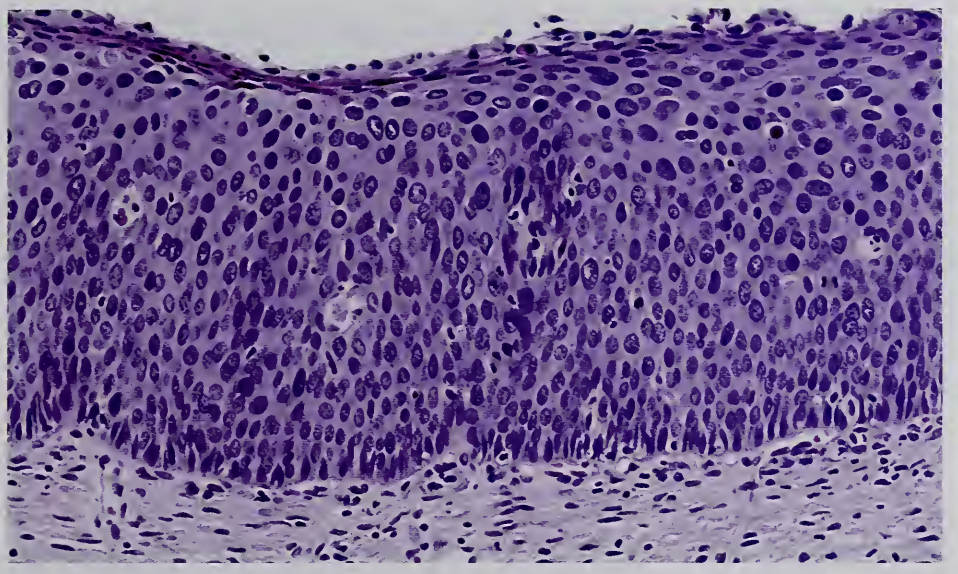


Figure 5-29

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CIN 3)

An immature monotonous proliferation of parabasal cells involves virtually the full thickness of the epithelium, with a thin atypical flattened layer partially involving the surface.

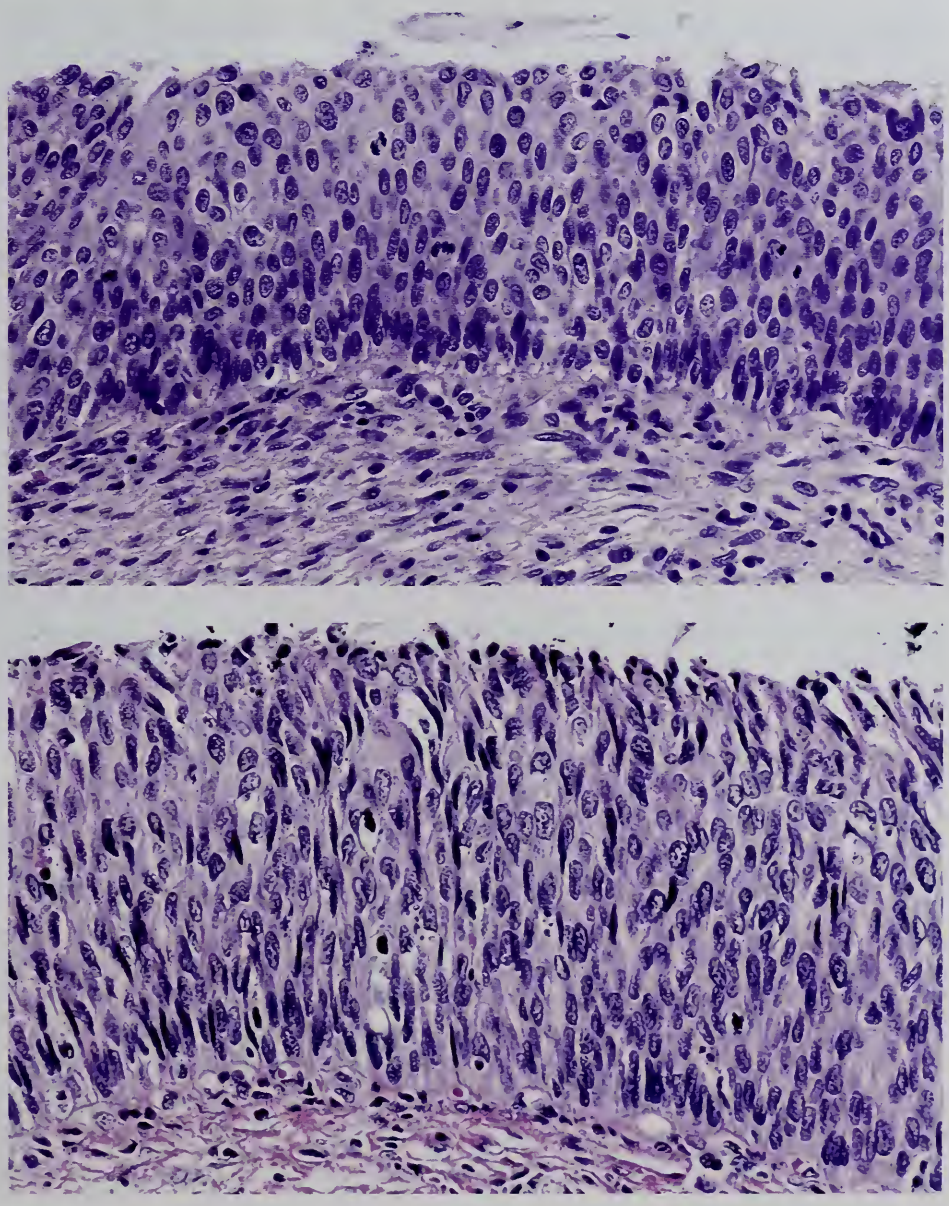


Figure 5-30

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CIN 3)

Top: An immature monotonous proliferation of parabasal cells is characterized by nuclei with granular hyperchromasia and mitotic figures in the middle and upper levels of the epithelium.

Bottom: Atypical cells involving the full thickness of the epithelium have an elongated, spindled appearance.

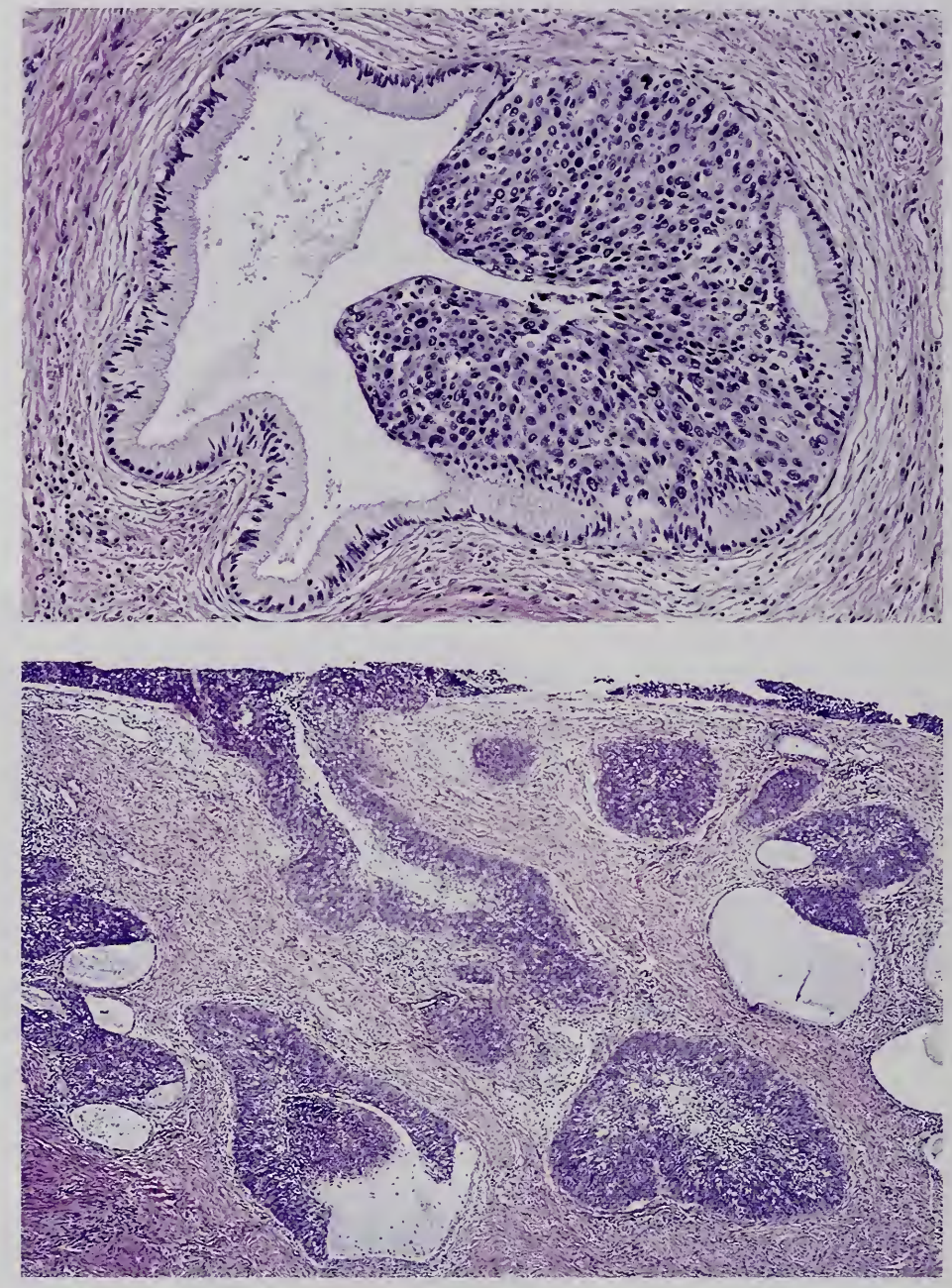


Figure 5-31

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION WITH ENDOCERVICAL GLAND INVOLVEMENT

Top: HSIL undermines the glandular epithelium and partially replaces the gland space.

Bottom: Endocervical glands are partially to completely replaced by HSIL. When extensive, the presence of rounded contours distinguishes gland involvement from the irregular, maturing nests of microinvasive squamous cell carcinoma.

Immunohistochemical Findings. Proliferation-associated antigens such as Ki-67 (MIB-1) (176) or the recently described antigens Cdc6 and Mcm5 (related to DNA replication) highlight cells with active DNA replication (429) but they do not distinguish dysplastic proliferating cells from normal proliferating cells. Despite this limitation, immunohistochemical assessment of the Ki-67 proliferation index is useful for distinguishing SIL from atypical immature metaplasia and atrophy (125,277). SILs have proliferating cells in the middle and upper levels of the epithelium (figs. 5-18, 5-32). Increasing indices and activity in the higher levels of the epithelium correlate with the grade of the lesion. In contrast, atrophy and immature metaplasia have proliferative activity confined to the immediate parabasal layer as in normal epithelium. Expression of the MN antigen, a transmembrane glycoprotein containing a carboanhydrase domain, has been linked to the malignant phenotype and has been observed in SIL and cervical carcinoma. Although the specificity appears to be high it does not stain all cervical cancers or their precursors and also stains normal endocervical cells (241).

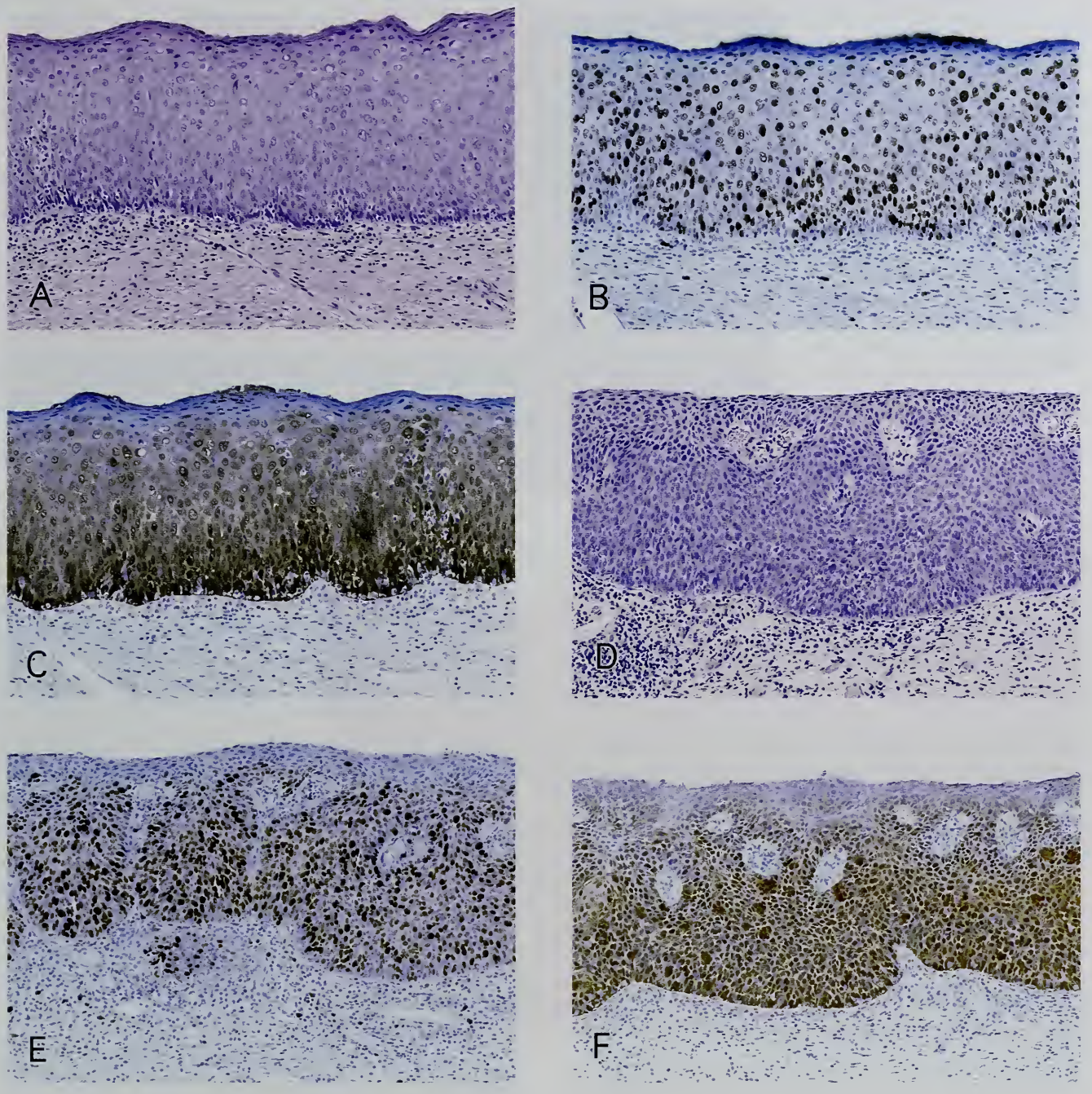


Figure 5-32

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CIN 2, CIN 3)

A: An atypical parabasal proliferation extends into the middle and upper third of the epithelium, consistent with HSIL/CIN 2).

B: Proliferation index, assessed by immunohistochemical expression of Ki-67, is markedly increased, with numerous positive nuclei distributed in all layers (deeper section of lesion in A).

C: Diffuse expression of p16 in the epithelium is characteristic of high-risk HPV-related HSIL (deeper section of lesion in figure A). The extent of staining seen in this example and in D is required for p16 expression to be considered indicative of a high-risk HPV-related intraepithelial lesion.

D: An atypical parabasal proliferation involves the full thickness of the epithelium, consistent with HSIL/CIN 3.

E: Proliferation index, assessed by immunohistochemical expression of Ki-67, is markedly increased, with numerous positive nuclei distributed in all layers (deeper section of lesion in D).

F: Diffuse expression of p16 in the epithelium is characteristic of high-risk HPV-related HSIL (deeper section of lesion in D).

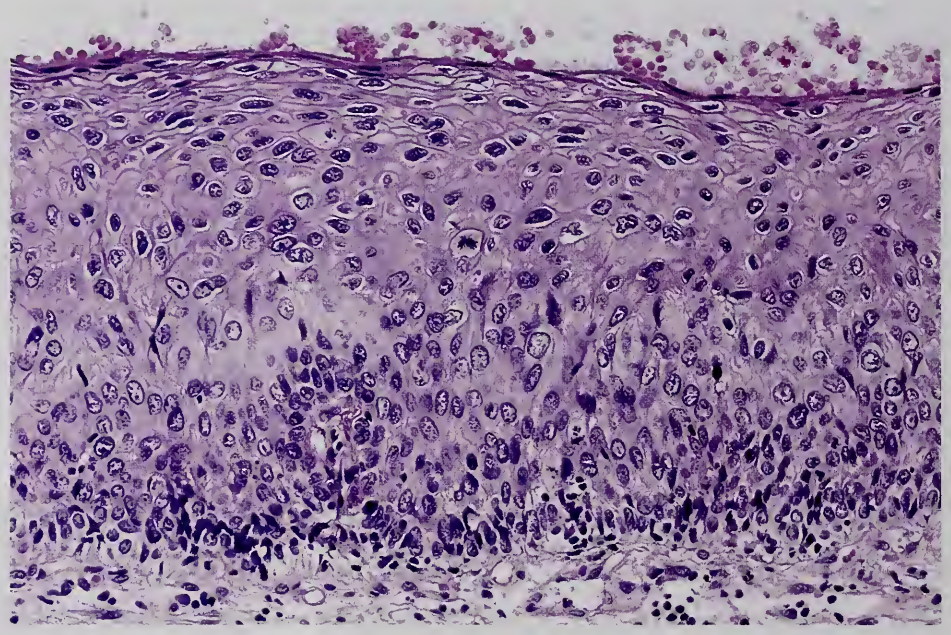


Figure 5-33

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CIN 2)

The features are borderline between LSIL/CIN 1 and HSIL/CIN 2: the upper half of the lesion suggests LSIL but mitotic figures in the middle and upper thirds qualify the lesion as HSIL/CIN 2.

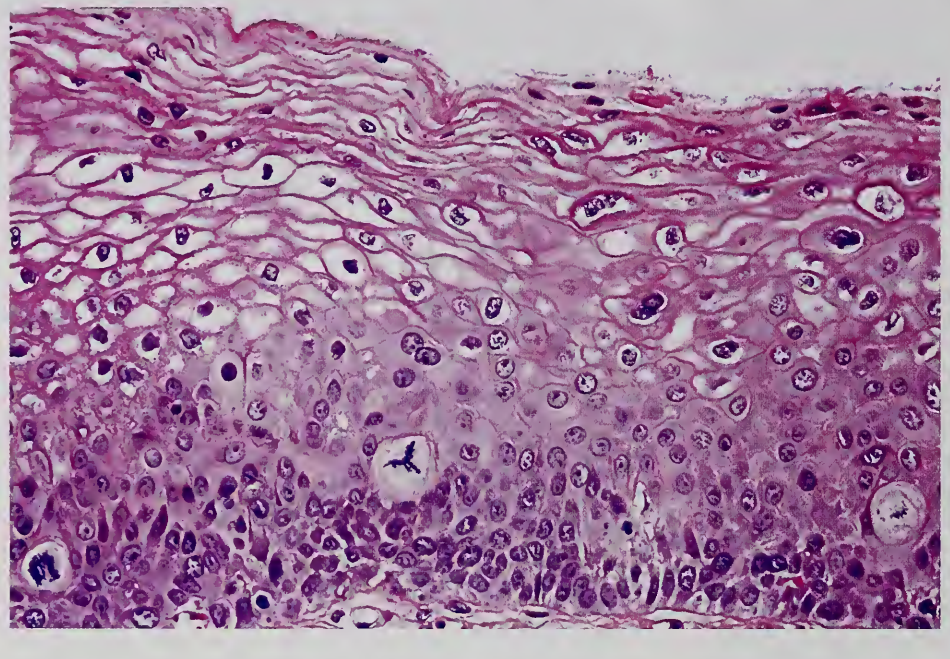


Figure 5-34

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CIN 1) VERSUS HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CIN 2)

The presence of abnormal mitotic figures is considered by some investigators as evidence of HSIL/CIN 2, however, most features indicate LSIL and therefore we would classify it as such.

More recently, *p16*, a gene expressed by the host cell in response to the overexpression of high-risk HPV oncogenes but not expressed in normal nontransformed cells, has been shown to be highly sensitive in the identification of all grades of SIL and cervical cancers (216). P16 expression has been shown to be associated with high-risk HPV infection in cervical squamous and glandular intraepithelial lesions as well as invasive cervical carcinomas, and is due to complex molecular mechanisms by which high-risk HPV transforming proteins interact with cell cycle regulatory proteins to generate a futile feedback loop resulting in p16 overexpression. Diffuse p16 expression can thus serve as a surrogate marker of high-risk HPV infection to identify these high-risk HPV-related cervical lesions (216a,349a,421a). LSILs are heterogeneous with respect to their p16 expression patterns, even when they contain high-risk HPV; some exhibit diffuse/strong p16 expression (often in the lower half of the epithelium, but sometimes involving the full thickness), whereas others exhibit focal/patchy expression or are even negative. They uniformly demonstrate some degree of increased proliferative activity as assessed by

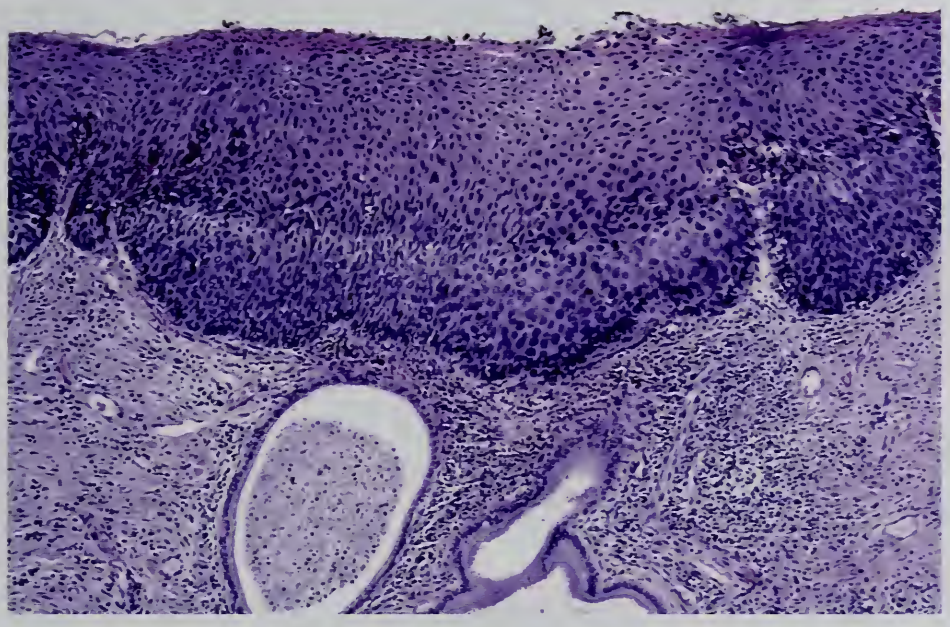


Figure 5-35

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION WITH LUGOL ARTIFACT

Sharply demarcated longitudinal zone of eosinophilic epithelium imparts a more mature appearance to the HSIL, making grading difficult. This artifact is due to the application of Lugol solution to the epithelium.

an immunostain for Ki-67. In contrast, HSILs are much more homogeneous with respect to their p16 expression patterns in that virtually all exhibit diffuse/strong p16 expression. They also almost always exhibit concordant p16 and Ki-67 expression patterns (namely, diffuse/strong p16 expression coupled with notably increased proliferative activity) (figs. 5-18, 5-32, 5-42–5-44). Immature metaplasia and atrophy lack p16 expression, and lesions related to low-risk HPV infection (condylomas and a minority of LSILs) exhibit only patchy, weaker expression of p16. To be considered positive, p16 immunostaining must be strong and diffuse.

HPV Studies. The immunohistochemical detection of HPV capsid antigen is of no value clinically. Although it works satisfactorily with commercially available reagents on formalin-fixed, paraffin-embedded tissue, it is insensitive. In situ hybridization for HPV can assist in the distinction of SIL from reactive atypia and atrophy but is limited by technical factors and availability in routine practice.

Differential Diagnosis. A number of non-HPV–related lesions may be confused with SIL. Immature metaplasia, lesions interpreted as atypical immature metaplasia but not associated with HPV infection (88,125,311), atrophy (fig. 5-44), and transitional metaplasia are the lesions that can simulate HSIL. Transitional metaplasia is discussed above (see Transitional Metaplasia). In immature metaplasia and those immature metaplasias interpreted as atypical but unrelated to HPV infection (both also discussed above), the full thickness of the epithelium is composed of immature parabasal cells with a high nuclear-cytoplasmic ratio. The cells are usually vertical and the nuclei are regular with even chromatin or mild hyperchromasia; nuclear pleomorphism is lacking. Immature metaplasia may have mitotic activity, but it is generally low, and abnormal mitotic figures are not present. In addition, cellular polarity is retained, cell membranes are clearly defined, and cellular crowding is not marked. A preserved layer of endocervical mucinous epithelium is often present on the surface of immature metaplastic squamous epithelium but only rarely overlies HSIL. Immunohistochemistry (Ki-67 and p16) is useful in the differential diagnosis (see above).

Atrophic epithelium is occasionally difficult to distinguish from HSIL because it is composed of basal and parabasal cells showing no maturation. Although there is a high nuclear-cytoplasmic ratio, atrophic epithelium is thin and shows no nuclear pleomorphism, mitotic activity, atypia, or lack of polarity. In older women, in whom it is difficult to distinguish atrophy from HSIL, a repeat biopsy after a 2-week course of daily-applied vaginal estrogen should resolve the problem by inducing maturation in atrophic epithelium. In contrast, estrogen administration does not alter the appearance of HSIL. Immunohistochemistry (Ki-67 and p16) is useful in the

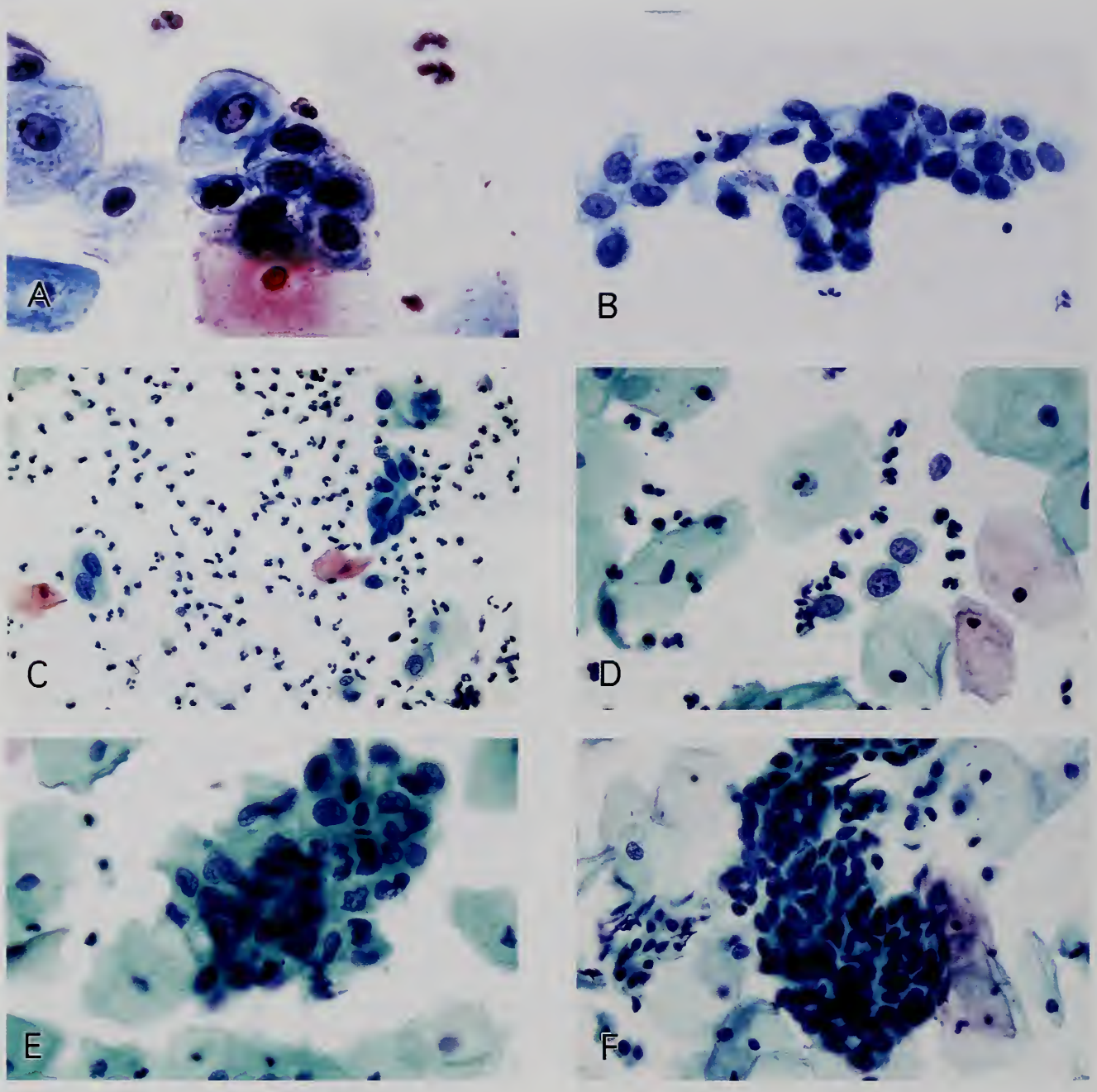


Figure 5-36

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CIN 2, CIN 3)

A: Conventional cytologic preparation contains atypical metaplastic type cells with increased nuclear-cytoplasmic ratios, vacuolated cytoplasm, nuclear hyperchromasia, granular chromatin, and irregular nuclear membranes, consistent with HSIL/CIN 2.

B: Conventional cytologic preparation demonstrates atypical metaplastic type cells with very high nuclear-cytoplasmic ratios, delicate cytoplasm, nuclear hyperchromasia, and irregular nuclear membranes, consistent with HSIL/CIN 3.

C: Liquid-based cytologic preparation contains atypical metaplastic type cells with sufficiently increased nuclear-cytoplasmic ratios, nuclear hyperchromasia, and irregular nuclear membranes to qualify as HSIL.

D: Small, atypical metaplastic cells from HSIL may be inconspicuous and only mildly hyperchromatic in liquid-based cytologic preparations.

E: Liquid-based cytologic preparation demonstrates a cellular aggregate containing crowded, atypical metaplastic type cells with high nuclear-cytoplasmic ratios, irregular nuclear membranes, granular chromatin, and nuclear hyperchromasia.

F: Syncytial fragments in a liquid-based cytologic preparation contain crowded, atypical metaplastic type cells with high nuclear-cytoplasmic ratios and marked nuclear hyperchromasia.

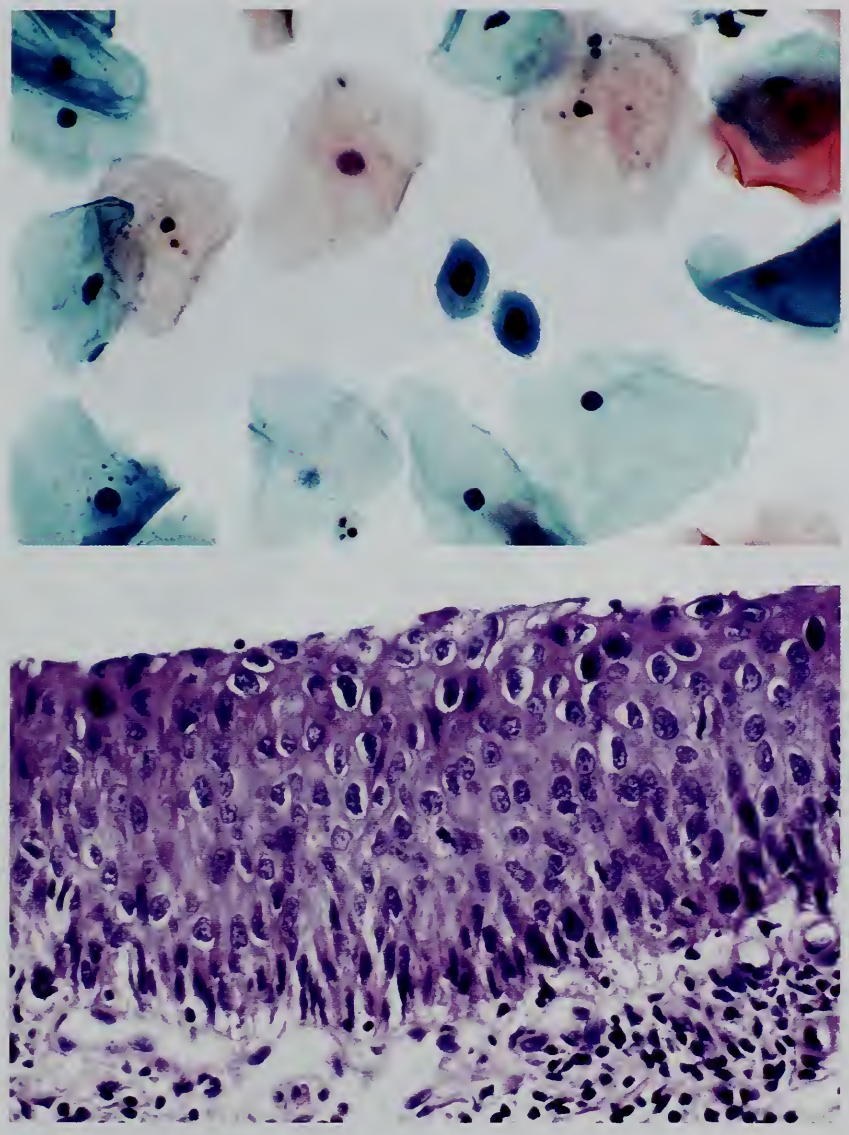


Figure 5-37

ATYPICAL SQUAMOUS METAPLASTIC CELLS, CANNOT EXCLUDE HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (ASC-H)

Top: Two atypical metaplastic cells suggest HSIL/CIN 2 but are insufficient to establish that diagnosis.

Bottom: Follow-up biopsy of the lesion seen in the left figure demonstrates HSIL/CIN 2.

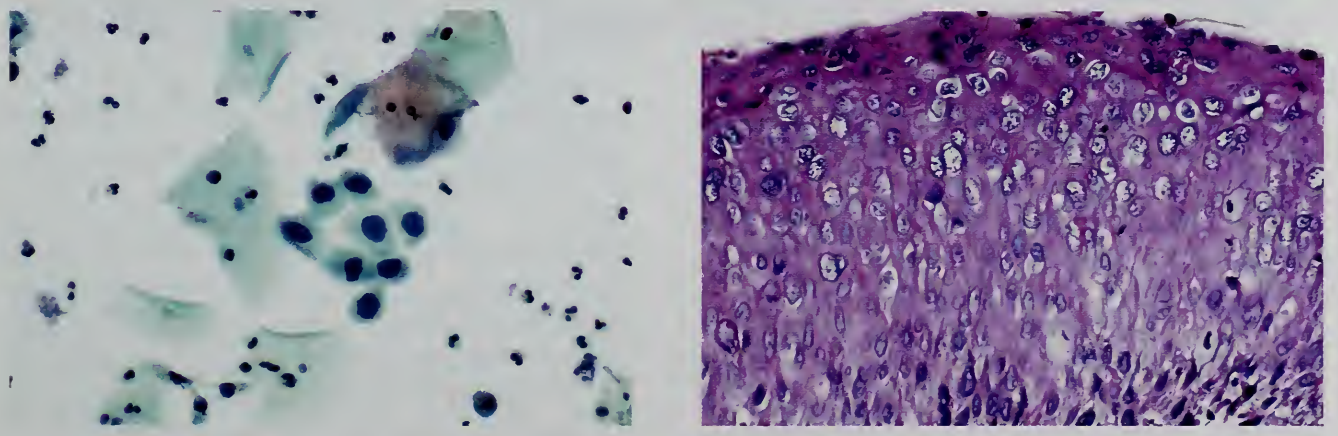


Figure 5-38

ATYPICAL SQUAMOUS METAPLASTIC CELLS, CANNOT EXCLUDE HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION

Left: A group of atypical metaplastic cells suggests HSIL/CIN 2 but nuclear abnormalities are insufficient to definitively establish that diagnosis.

Right: Follow-up biopsy of the lesion seen on the left demonstrates HSIL/CIN 2, metaplastic/eosinophilic type.

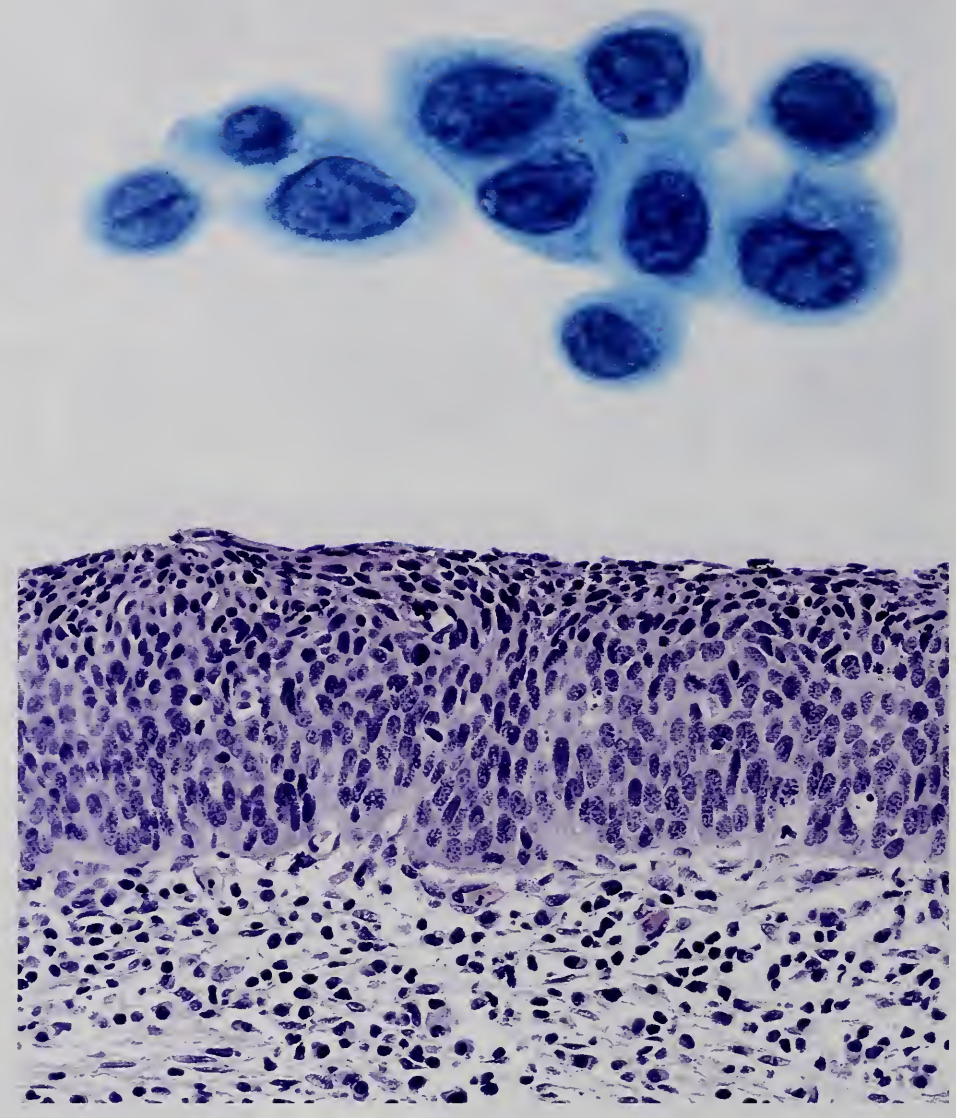


Figure 5-39

ATYPICAL SQUAMOUS METAPLASTIC CELLS

Top: Atypical squamous metaplastic cells favor HSIL.

Bottom: Follow-up biopsy of the lesion seen above demonstrates HSIL/CIN 3.

differential diagnosis and obviates the need for estrogen treatment in almost all instances.

Reparative processes may also be misinterpreted as HSIL. In reparative processes, atypical parabasal cells occupy the lower levels of the epithelium but the cells tend to be uniform in size and usually have distinct cell membranes. The nuclei have smooth outlines and prominent nucleoli. Mitotic activity is generally low. In addition, a dense acute and chronic inflammatory infiltrate is often present.

Normal metaplastic squamous epithelium with prominent glycogen vacuolization is often confused with LSIL. In contrast to LSIL, the nuclei in these cells are not enlarged or atypical (fig. 5-45). Perinuclear clearing by itself may be associated with a variety of infectious microorganisms, notably *Trichomonas vaginalis* (225). In addition to the absence of nuclear atypia, normal stratification and maturation are maintained in such infections, whereas in LSIL, there is some degree of cellular disorganization, particularly near the surface, and there is a disturbance in the normal pattern of maturation.

Clinical Behavior. Numerous studies, both retrospective and prospective, performed with the aim of determining the behavior of SIL have reported widely different estimates of the rate of progression and regression. The differences reported by the various studies are due, in large

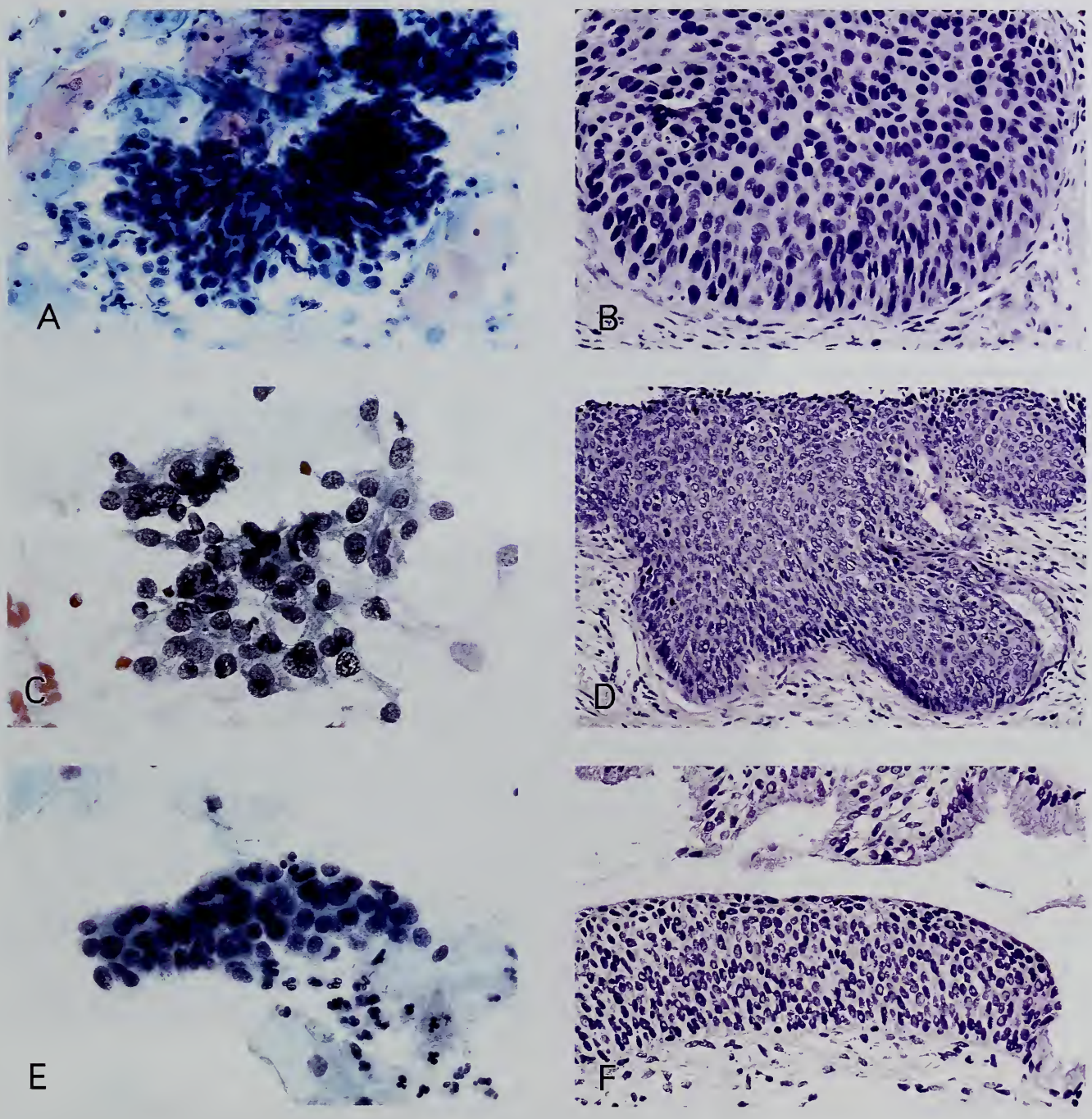


Figure 5-40

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION

A: In cytologic preparations, syncytial aggregates of HSIL suggest endocervical gland involvement.

B: Follow-up biopsy of the lesion seen in A demonstrates HSIL within an endocervical gland.

C: Delicate cytoplasm and a honeycomb arrangement can lead to interpretation of atypical immature squamous metaplastic cells as atypical glandular cells, endocervical type, in cytologic specimens.

D: Follow-up biopsy of the lesion seen in C demonstrates HSIL/CIN 3 involving endocervical glands rather than a true endocervical glandular intraepithelial lesion.

E: Delicate, vacuolated cytoplasm and a suggestion of a honeycomb arrangement can lead to interpretation of atypical immature squamous metaplastic cells as atypical glandular cells, endocervical type, in cytologic specimens.

F: Follow-up biopsy of the lesion seen in E demonstrates HSIL/CIN 3 involving an endocervical gland.

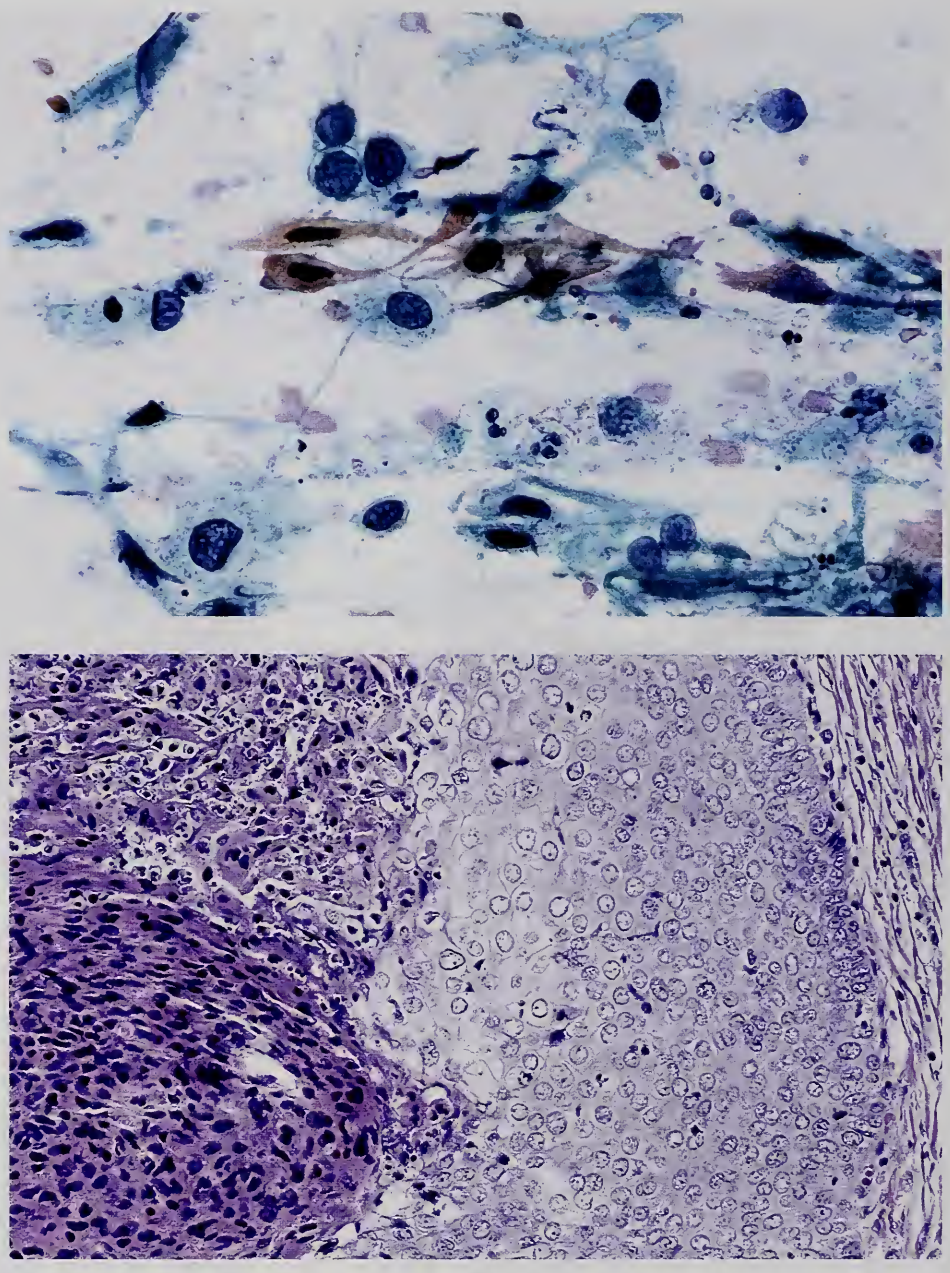


Figure 5-41

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION, KERATINIZING TYPE

Top: Atypical keratinized cells and some granular background material suggest invasive squamous cell carcinoma.

Bottom: Follow-up biopsy of the lesion seen in the left figure demonstrates HSIL involving an endocervical gland with abnormal keratinized surface epithelium filling the gland lumen; no invasion was identified in the excisional specimen.

part, to differences in study design and in the nature of the populations under investigation. For example, it has been argued that the diagnostic biopsy, by removing or destroying most of the lesion, may give a false impression of the natural history of the disease. The effect of a biopsy on the behavior of SIL was evaluated in a long-term follow-up study performed in Sweden by Nasiell et al. (285,286). In this study, 555 women with LSIL (CIN 1) and 894 women with HSIL (CIN 2) were followed on average for 39 and 78 months, respectively. In women with CIN 2, the punch biopsy decreased the frequency of progression and increased the frequency of regression. Nonetheless, even in patients whose lesions were not biopsied, regression occurred in 50 percent of the cases, progression to CIN 3 in 35 percent, and persistence in 15 percent. Compared with the incidence of CIN 3 in this population, the risk of progression to CIN 3 for a woman with CIN 2 was about 2,000 times greater than for a woman without CIN.

In women with LSIL (CIN 1), regression occurred in 62 percent of the cases, progression to CIN 3 in 16 percent, and persistence as CIN 1 in 22 percent (286). Biopsies did not alter the

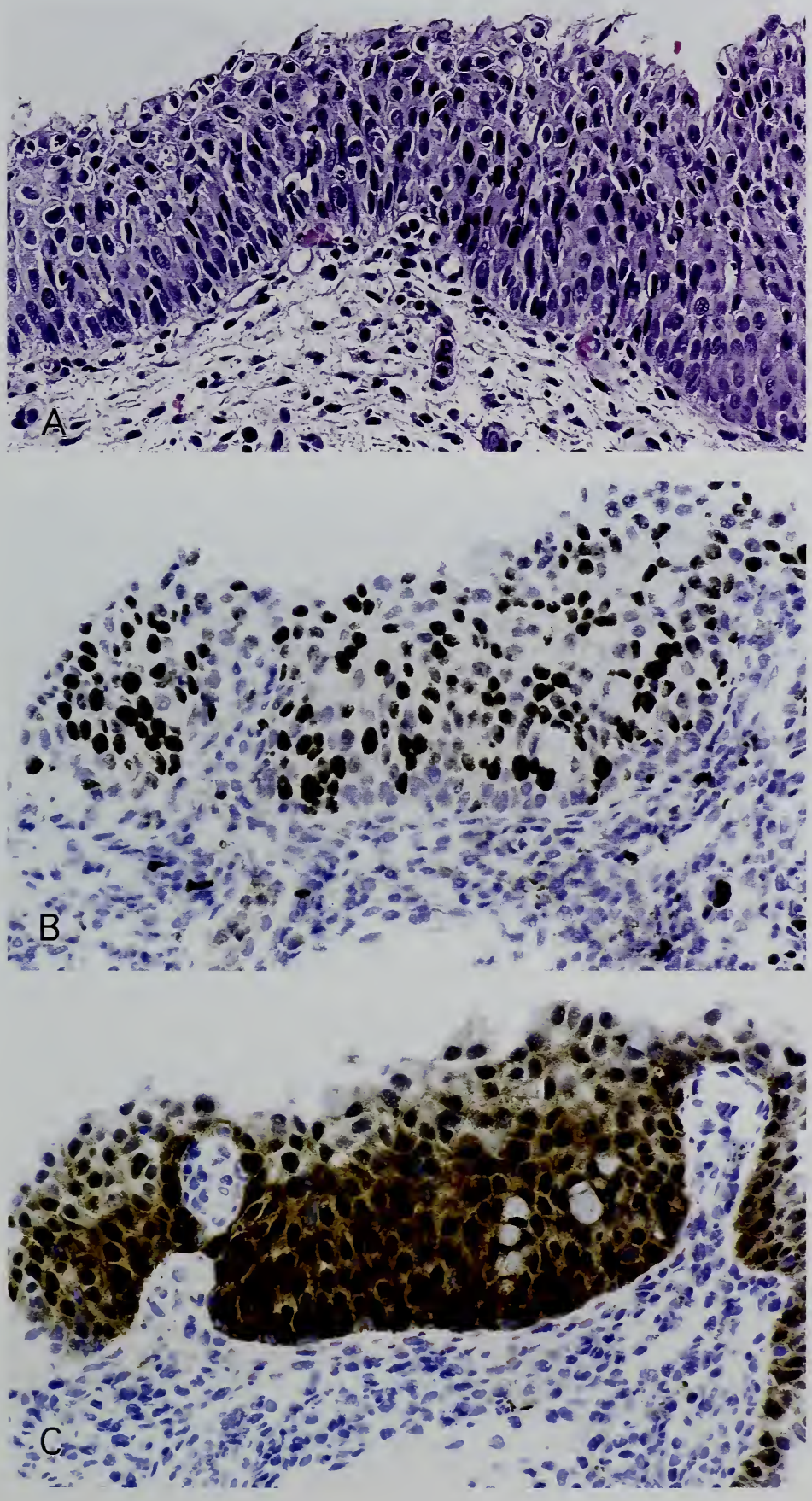


Figure 5-42

ATYPICAL IMMATURE METAPLASIA, FAVORING HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION

A: Thin, immature metaplastic epithelium lacks evident mitotic activity but nuclear atypia and cellular disarray are sufficient to favor a diagnosis of HSIL.

B: Immunohistochemical stain for Ki-67 performed on a deeper section of the lesion demonstrates an increased proliferation index with positive nuclei in all levels of the epithelium.

C: Immunohistochemical stain for p16 performed on a deeper section of the lesion demonstrates diffuse strong staining of the lesional epithelium, consistent with a high-risk HPV-related HSIL.

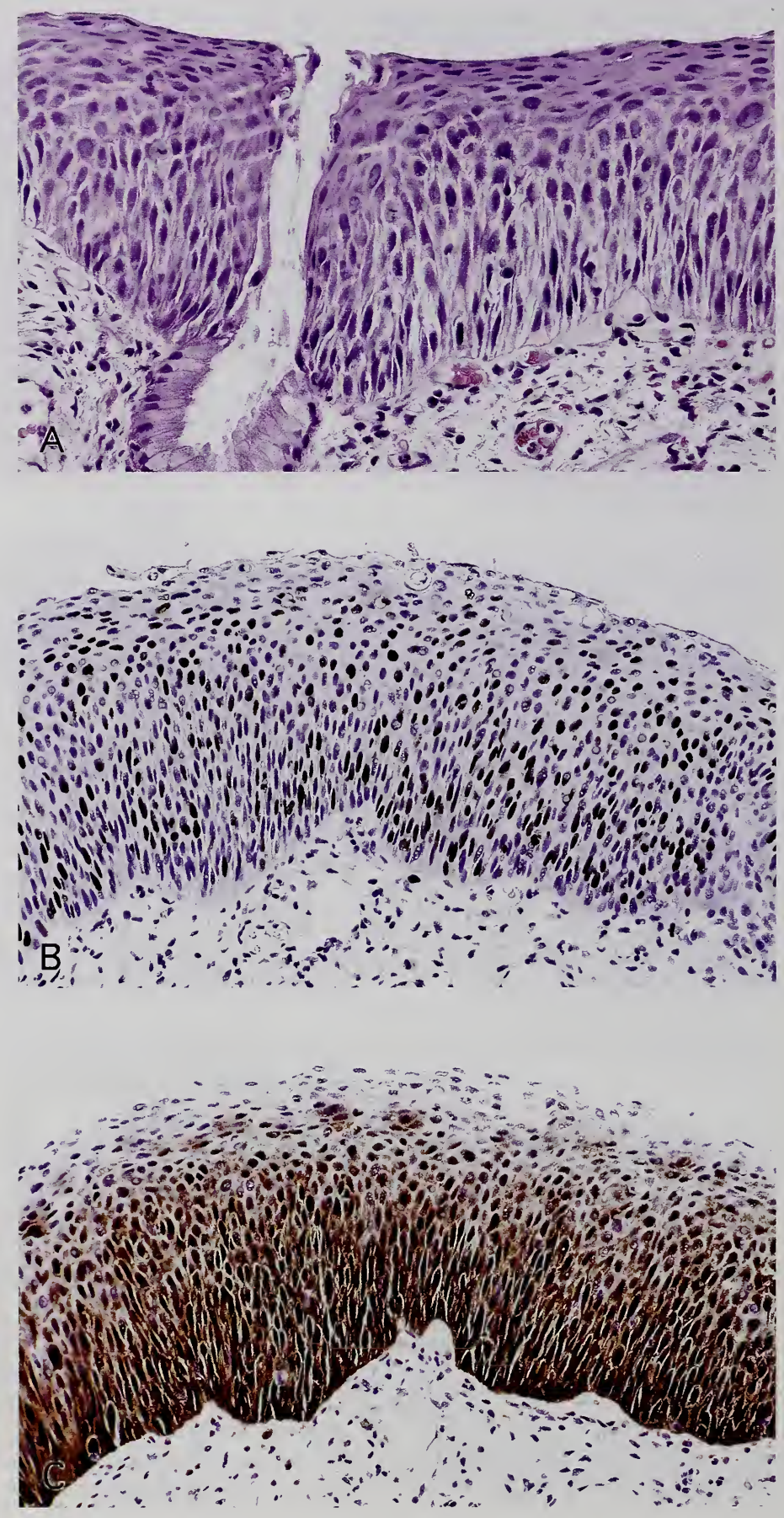


Figure 5-43

ATYPICAL IMMATURE SQUAMOUS METAPLASIA, FAVORING HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION

A: Atypical metaplastic epithelium has minimal mitotic activity and the spongiotic appearance suggests the possibility of a reactive process but nuclear pleomorphism and cellular disarray suggest HSIL.

B: Immunohistochemical stain for Ki-67 performed on a deeper section of the lesion demonstrates an increased proliferation index with positive nuclei in all levels of the epithelium.

C: Immunohistochemical stain for p16 performed on a deeper section of the lesion demonstrates diffuse strong staining of the lesional epithelium, consistent with a high-risk HPV-related HSIL.

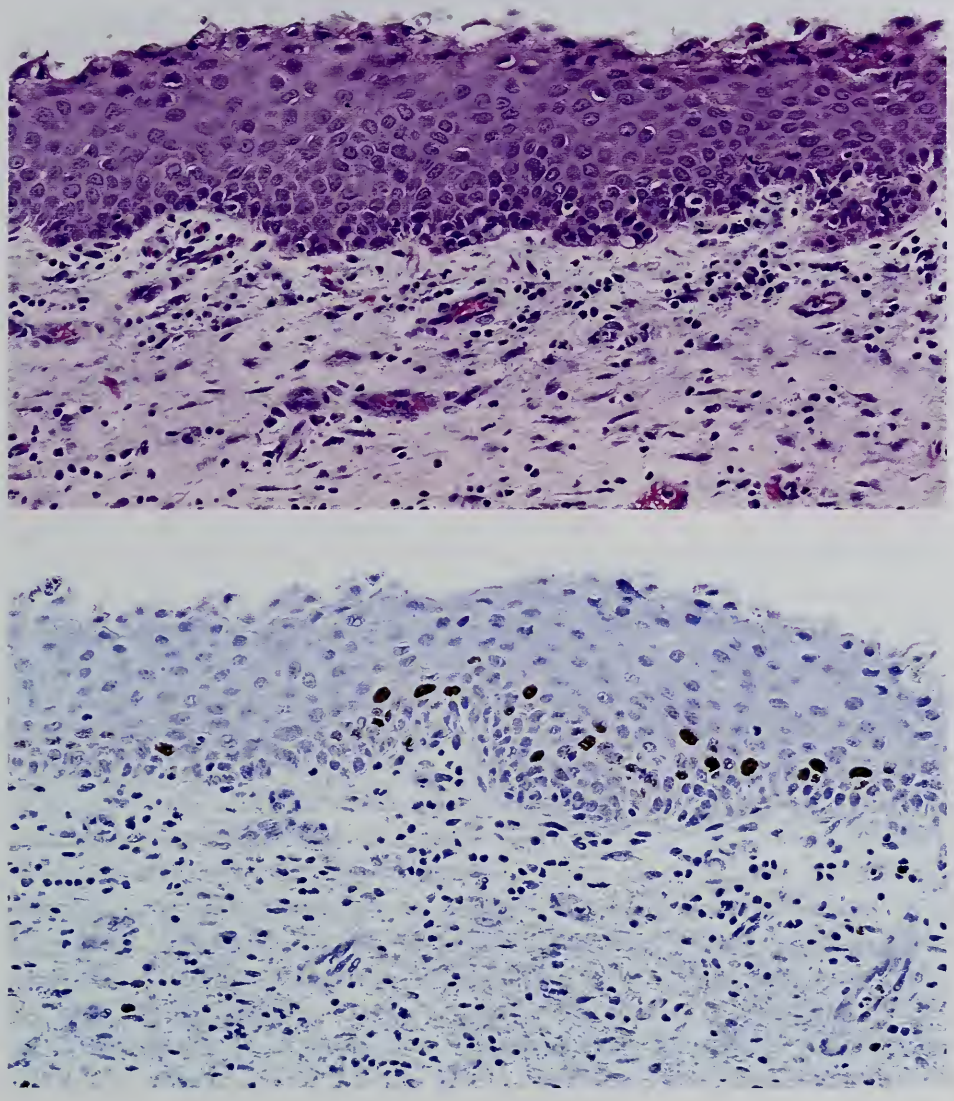


Figure 5-44

ATROPHY

Top: The squamous mucosa is composed only of parabasal cells and thus lacks maturation, suggesting the possibility of HSIL, but nuclear pleomorphism and mitotic activity are absent.

Bottom: Immunohistochemical stain for Ki-67 performed on a deeper section of the lesion demonstrates a low proliferation index, with positive cells confined to the parabasal layer.

outcome of LSIL (CIN 1). The risk of progression of CIN 1 to CIN 3 was about 560 times greater than in women without CIN. Other studies have reported that HSIL (CIN 3), when left untreated, has significant invasive potential, progressing to invasive cancer in approximately 20 percent of cases (220,267). Thus, the consensus is that LSIL may regress, persist, or progress to invasive cancer. The outcome for an individual lesion cannot be predicted with certainty but as a group, low-grade lesions are more likely to regress and high-grade lesions are more likely to persist or progress (63,64,114,291,317,357,388).

A study from a large cytology laboratory in Toronto, Canada, which linked their cytology records with the Ontario Tumor Registry from 1962 to 1980 reported after 10 years of follow-up, only 12 percent of untreated mild dysplasia and 17 percent of untreated moderate dysplasia lesions progressed to carcinoma in situ (165). The remaining cases had all regressed. The high regression rate of CIN 2 in this study is unusual and it is conceivable that the criteria used for making that diagnosis were quite liberal. Generally, HSIL has a much higher risk of progressing than LSIL. Long-term retrospective studies have reported progression of carcinoma in situ in 22 to 72 percent of cases. In an unusual prospective study, McIndoe et al. (265) reported progression of carcinoma in situ to invasive cancer in 29 percent of patients followed from 1 to 20 years.

Although traditionally it has been believed that high-grade lesions progress from low-grade lesions, some investigators believe that HSIL lesions do not evolve from LSIL, but rather, are established at the outset as high-grade lesions

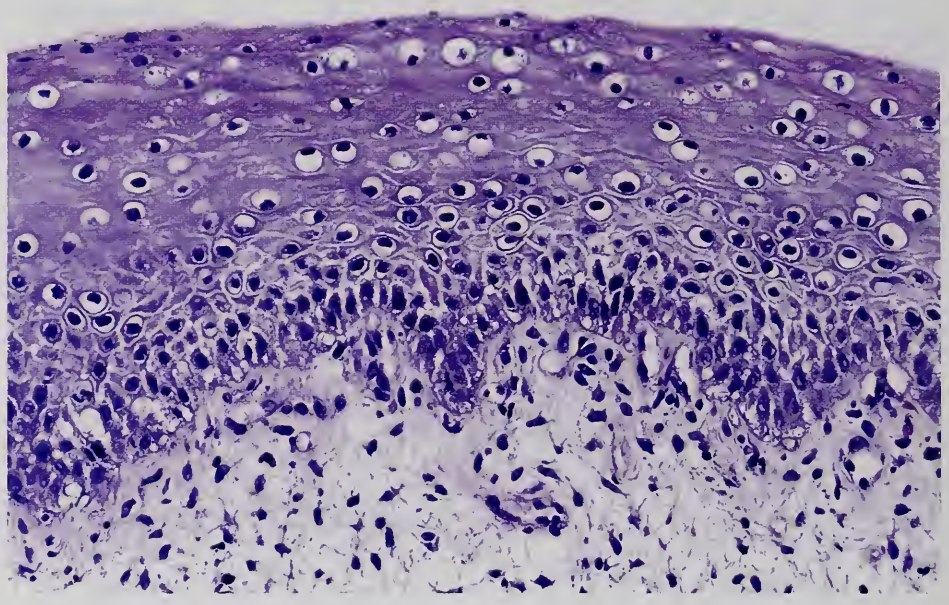


Figure 5-45

GLYCOGENATED MATURE SQUAMOUS METAPLASIA

Intracytoplasmic glycogen creates cytoplasmic clearing which simulates koilocytosis but cells lack the nuclear changes required for a diagnosis of LSIL.

(54,214). These investigators maintain that lesion grade is influenced by location, namely, that SIL developing on the ectocervix tends to be low grade whereas SIL developing in the endocervical canal tends to be high grade. According to this view, apparent progression of a low-grade lesion reflects the evolution of two concurrently established lesions with different natural histories. The majority of low-grade lesions spontaneously regress, whereas the high-grade lesions are less likely to do so. Since high-grade lesions may be small and high in the canal, they may be more easily missed while a simultaneous low-grade lesion on the ectocervix is detected. This view is supported by the results of a natural history study (227). Among 241 cytologically normal women enrolled at a sexually transmitted disease (STD) clinic, 26 women developed biopsy-confirmed HSIL within the first 12 months of follow-up. These lesions developed in the absence of preceding cytologically detectable LSIL despite careful monitoring with cytology and colposcopy performed every 3 months. In another study of women infected with high-risk HPV types, it was found that 88 percent of the cases of SIL were first identified as HSIL (293).

A study utilizing comparative genomic hybridization found that chromosome 3q is overrepresented in 90 percent of invasive squamous cell carcinomas and undergoes a high-level copy number increase (amplification) (164). In addition, a gain of chromosome 3q is detectable in a CIN 3 lesion, suggesting that this chromosomal alteration is a pivotal aberration in the transition from CIN 3 to invasive cancer.

Treatment. It is estimated that 50 million Pap smears are performed annually in the United States and more than 5 percent are abnormal. HSIL accounts for approximately 0.5 percent of all Pap smear interpretations and there is a general consensus that these lesions should be evaluated by colposcopy and biopsy. Until recently, the management of ASC-US and LSIL was controversial, with some health care providers advocating conservative follow-up with Pap smears and others favoring colposcopy and biopsy. Recent studies reported from the ASCUS/LSIL Triage Study (ALTS) have provided important insights into the management of these low-grade cytologic abnormalities (382). Using a commercially available HPV DNA test, Hybrid Capture 2™ (HC2) for the detection of high-risk HPV types, and thin-layer cytology, the ALTS investigators reported that nearly 50 percent of ASC-US lesions were HPV positive. Among women with ASC-US, the underlying prevalence of histologically confirmed CIN 3 was 5.1 percent. Moreover, the sensitivity of HC2 to detect CIN 3 or squamous carcinoma was 96.3 percent, which was greater than a single additional cytologic test indicating ASC-US or higher grade and of comparable specificity (382). Accordingly, it was recommended that HC2 testing for high-risk HPV DNA is an appropriate method of managing women with ASC-US. In contrast, the ALTS found that over a 2-year period following the cytologic

diagnosis of LSIL, histologically confirmed CIN 3 was found in 15 percent of women but over 80 percent of the LSIL cytologic specimens were HPV positive. It was therefore concluded that HPV testing was not a useful triage strategy for the cytologic diagnosis of LSIL and it has been recommended that women with LSIL are best managed by colposcopy (382).

As LSIL is not an immediate precursor of invasive cervical cancer but HSIL is, the ALTS attempted to determine the risk of histologically confirmed HSIL (CIN 2 or 3) according to colposcopy and directed biopsy findings among women with LSIL or HPV-positive ASC-US cytology (83). The risk of developing HSIL in 2 years was the same (27 percent) for LSIL and HPV-positive ASC-US, indicating that these diagnoses, in essence, are slightly different cytologic manifestations of the same disease process. Furthermore, after excluding women with a histologic diagnosis of CIN 2 or 3 at initial colposcopy and biopsy (18 percent), the remaining women were at nearly identical risk for subsequent CIN 2 or 3 (12 percent) regardless of whether they had negative colposcopy, negative colposcopically directed biopsy, or CIN 1 on biopsy. In a companion study, the ALTS found that for women with cytologic LSIL or HPV-positive ASC-US following colposcopic findings of CIN 1 or negative colposcopy, an HPV test at 12 months was the most efficient method of identifying CIN 2 or 3 (148). HPV testing at 12 months had a sensitivity of 92 percent for detection of CIN 2 or 3. Repeat semiannual cytology with referral to colposcopy at an ASC-US threshold had a slightly lower sensitivity but had a much higher rate of colposcopy referral.

High-grade lesions are treated by electrocautery loop excision (LEEP), cervical cone (cold knife) biopsy, or rarely, hysterectomy. Therapy is based on the size and extent of the lesion, the experience of the gynecologist with various techniques, and the desires of the patient. Generally, large lesions tend to be of higher grade and involve more of the endocervical canal.

Long-term follow-up studies indicate that there is a low but significant recurrence rate of SIL after treatment. Although it would be expected that HSIL that was incompletely removed by a cone biopsy would be more likely to recur than one that was completely excised, a study of 948 patients with CIN 3 reported that the development of subsequent invasive disease was not influenced by whether the lesion was completely excised (265). The most important predictor of recurrent disease was the follow-up cytology. Among 139 women with normal cytology after incomplete excision, invasive cancer later developed in 35 percent. In contrast, invasive carcinoma developed in 22 percent of women with persistently abnormal cytology, even when the original lesion had been completely removed. Women treated for SIL must therefore undergo long-term follow-up, because these investigators found that invasive cancer was 3.2 times more likely to develop in women treated for CIN 3 with normal follow-up by cytology than in women who had never had CIN 3. It has been shown that a positive HPV test is a more sensitive and specific indicator of recurrent disease than margin status or repeat cytology (310). Other studies have shown that although highly sensitive, testing for HPV lacks the specificity provided by cytology; these investigators advocated both cytology and HPV testing for the post-treatment follow-up of SIL (82).

Squamous Cell Carcinoma

Squamous cell carcinomas comprise all invasive neoplasms composed exclusively or almost exclusively of malignant squamous cells. These tumors are broadly divided into two categories: 1) microinvasive carcinomas, which invade the cervical stroma to a limited extent, and 2) frankly invasive carcinomas, which invade to a depth beyond the limits used to define microinvasive carcinoma. In view of the importance of microinvasive carcinoma from the standpoint of diagnosis, treatment, and prognosis, and the controversy over its definition, this category is considered separately from frankly invasive squamous carcinoma.

Microinvasive Squamous Cell Carcinoma

Definition. A definition of *microinvasive squamous cell carcinoma* was introduced when investigators realized that carcinomas that invaded less than 5 mm into the stroma seldom metastasized. Subsequent studies relating the depth of invasion to survival or lymph node metastases led the Society of Gynecologic Oncologists (SGO) in 1974 to propose a definition of microinvasion as invasion of the stroma from the point of origin to a depth of 3 mm or less; lesions with

Table 5-1

STAGING OF CARCINOMA OF THE CERVIX UTERI

FIGO[a]			TNM Stages
		Primary tumor cannot be assessed	TX
		No evidence of primary tumor	T0
0		Carcinoma in situ (preinvasive carcinoma)	Tis
I		Cervical carcinoma confined to uterus (extension to corpus should be disregarded)	T1
	IA	Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions—even with superficial invasion—are stage IB/T1b	T1a
	IA1	Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread	T1a1
	IA2	Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less[b]	T1a2
	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2/T1a2	T1b
	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension	T1b1
	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension	T1b2
II		Tumor invades beyond the uterus but not to pelvic wall or to lower third of vagina	T2
	IIA	Without parametrial invasion	T2a
	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension[c]	T2a1
	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension[c]	T2a2
	IIB	With parametrial invasion	T2b
III		Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctioning kidney	T3
	IIIA	Tumor involves lower third of vagina no extension to pelvic wall	T3a
	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney	T3b
	IVA	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis[d]	T4
	IVB	Distant metastasis	M1

[a]FIGO = International Federation of Gynecology and Obstetrics.
[b]The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.
[c]Data from references 101a and 380a.
[d]The presence of bullous edema is not sufficient to classify a tumour as T4.

vascular/lymphatic invasion are excluded from the category. Other studies demonstrated that the volume of tumor is a very useful parameter of metastatic potential (55,56) but the method by which volume is determined requires hemisecting the cone biopsy and then processing all of the tissue in serial step sections. Several studies have shown, however, that measuring the depth of invasion, the lateral extent of invasion, and the presence of vascular/lymphatic invasion accurately predict the likelihood of lymph node metastases (35,251,358,377,415).

Most patients who die of disseminated squamous cell carcinoma have either vascular/lymphatic involvement, tumors that invade more than 5 mm in the cervical stroma, or tumors that are greater than 2.5 cm^3. In 2000, the International Federation of Gynecology and Obstetrics (FIGO) classification defined a stage IA tumor as one that invades to a "depth of no more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates and that the horizontal extent of the tumor does not exceed 7 mm" (Tables 5-1, 5-2). Tumors that qualify as stage IA are further subdivided into those that invade up to 3 mm into the cervical stroma (stage IA1) and those that invade more than 3 mm, but not more than 5 mm (stage IA2). Lesions of greater size are stage IB. The diagnosis of both stages IA1 and IA2 is based on microscopic examination of a cone biopsy which must include the entire lesion. For many gynecologic oncologists, only stage IA1 tumors are referred to as microinvasive carcinoma. Vascular/lymphatic space involvement does not alter the staging but should be

Table 5-2

STAGE GROUPING OF CARCINOMA OF THE CERVIX UTERI

FIGO[a] Stage	UICC T	N	M
0	Tis	N0	M0
IA1	T1a1	N0	M0
IA2	T1a2	N0	M0
IB1	T1b1	N0	M0
IB2	T1b2	N0	M0
IIA	T2a	N0	M0
IIA1[b]	T2a1	N0	M0
IIA2[b]	T2a2	N0	M0
IIB	T2b	N0	M0
IIIA	T3a	N0	M0
IIIB	T1	N1	M0
	T2	N1	M0
	T3a	N1	M0
	T3b	Any N	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1

Regional Lymph Nodes (N)
NX – Regional lymph nodes cannot be assessed
N0 – No regional lymph node metastasis
N1 – Regional lymph node metastasis

Distant Metastasis (M)
MX – Distant metastasis cannot be assessed
M0 – No distant metastasis
M1 – Distant metastasis

[a]FIGO = International Federation of Gynecology and Obstetrics; UICC = Union International Contra Cancer.
[b]Data from references 101a and 380a.

specifically recorded because it affects treatment decisions. Tumors that fulfill the SGO definition of microinvasive carcinoma have almost no potential for metastasis or recurrence, and this definition appears to be the most appropriate one for guiding clinical management.

General Features. Although microinvasive carcinoma occurs in women from 20 to 70 years of age, the majority of women are 35 to 46 years of age. There is a wide variation in the reported prevalence, which undoubtedly reflects differences in the definition, methods of processing cone biopsies, and the criteria used for measuring depth of invasion. A population-based cervical cancer registry study from British Columbia estimated the prevalence of microinvasive carcinoma to be 4.8/100,000 women screened compared to the prevalence of carcinoma in situ which was 316/100,000 (34). Because LEEP is commonly performed on patients with SIL, better estimates of prevalence of microinvasive carcinoma with all grades of SIL have been obtained. Studies have reported colposcopically undetected microinvasive carcinoma in 0.4 to 3.0 percent of all patients with biopsy-confirmed SIL (281).

Most women with microinvasive carcinoma are asymptomatic. The tumors are generally detected as HSIL on a cervical cytologic specimen. In the past it has been asserted that colposcopists and cytopathologists could identify these lesions with a high degree of accuracy, but recent studies have challenged that claim. In a study of 536 women undergoing laser conization, cytology predicted the presence of invasion in only 27 percent of patients with microinvasion (17).

Gross Findings. The gross appearance of microinvasive carcinoma is similar to that of intraepithelial neoplasia, and is best appreciated on colposcopic examination. A variety of colposcopic patterns may be seen, but the presence of abnormal vessels is considered to be the most specific.

Microscopic Findings. Microinvasion is manifested by the presence of irregularly shaped tongues of epithelium that project from the base of an intraepithelial neoplasm into the stroma (figs. 5-46, 5-47). Usually, the intraepithelial lesion is HSIL, but in rare instances, the overlying epithelium resembles LSIL. In these cases, the abnormal cells in the overlying epithelium are confined to the basal and parabasal levels, whereas the superficial epithelium is mature. Typically, differentiation of the neoplastic cells occurs at the point of invasion. The invasive cells contain more abundant eosinophilic cytoplasm than the cells of the adjacent intraepithelial lesion, nuclei appear vesicular with prominent nucleoli rather than hyperchromatic, and cells may show keratinization (fig. 5-48). The margin of the invasive tumor is usually irregular. An accompanying desmoplastic reaction and inflammatory infiltrate may be evident. Vascular/lymphatic spaces are usually involved, especially by larger lesions. Because of shrinkage during tissue processing, it may be difficult

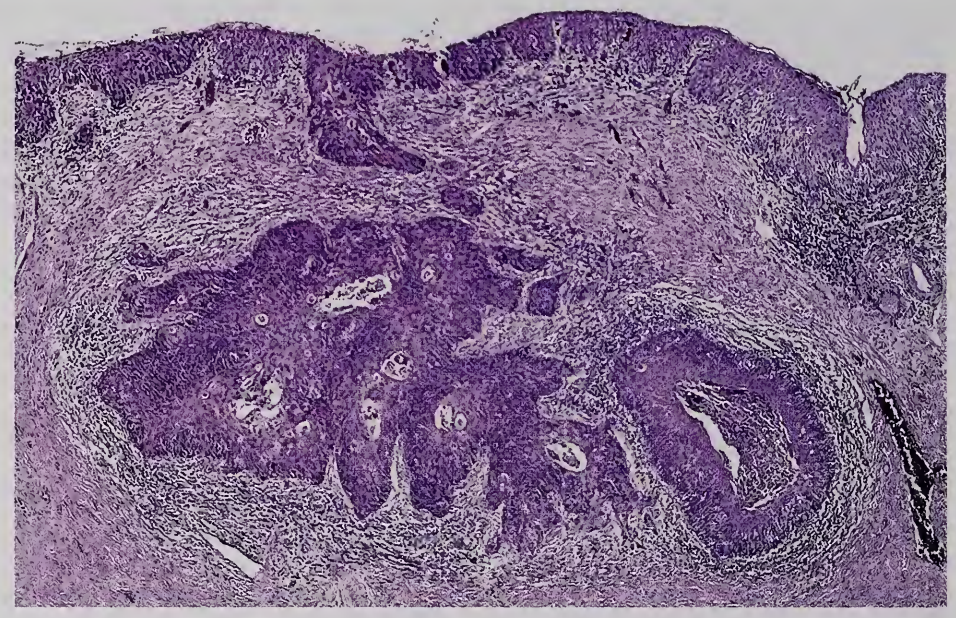


Figure 5-46

MICROINVASIVE SQUAMOUS CELL CARCINOMA

Irregularly shaped nests of squamous carcinoma in the superficial cervical stroma are surrounded by an inflammatory infiltrate; one nest is still connected to the overlying HSIL.

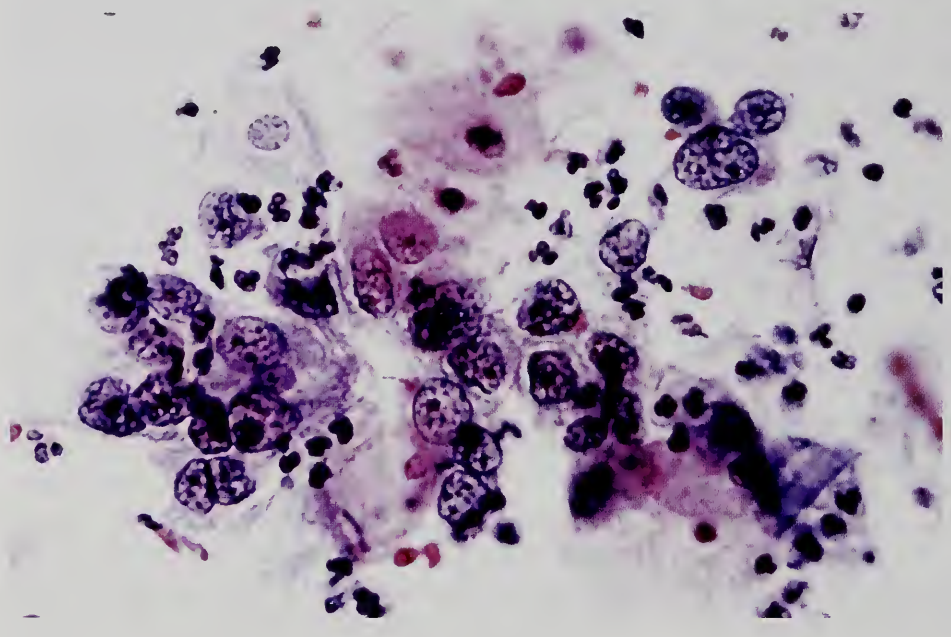


Figure 5-47

MICROINVASIVE SQUAMOUS CELL CARCINOMA

Markedly atypical squamous cells with increased cytoplasm and vesicular nuclei with nucleoli can suggest the possibility of microinvasion in a cytologic preparation but definitive diagnosis should be reserved for a tissue specimen.

to differentiate vascular invasion from tissue retraction around tumor nests. Immunohistochemical assessment for the presence of vascular endothelial markers, such as CD34 and CD31, in cells lining the tissue spaces can facilitate the distinction.

The growth pattern of microinvasive carcinoma is usually described as finger-like or confluent. Involvement of the margin of an excisional specimen (LEEP or cone biopsy) by invasive carcinoma or even by HSIL precludes a diagnosis of microinvasive carcinoma because additional, possibly deeper invasion may be present higher in the endocervix. Both the depth of and lateral extent of the microinvasive squamous carcinoma should be measured because these measurements determine whether the lesion qualifies for the diagnosis, and if so, these measurements are used to determine treatment (fig. 5-49).

Differential Diagnosis. Microinvasion can be confused with HSIL or even immature squamous metaplasia involving the endocervical glands, particularly when the latter two processes are extensive or when tangential sectioning or crush artifacts are present. The presence of rounded contours distinguishes endocervical glands involved by HSIL from the irregular nests of microinvasive squamous cell

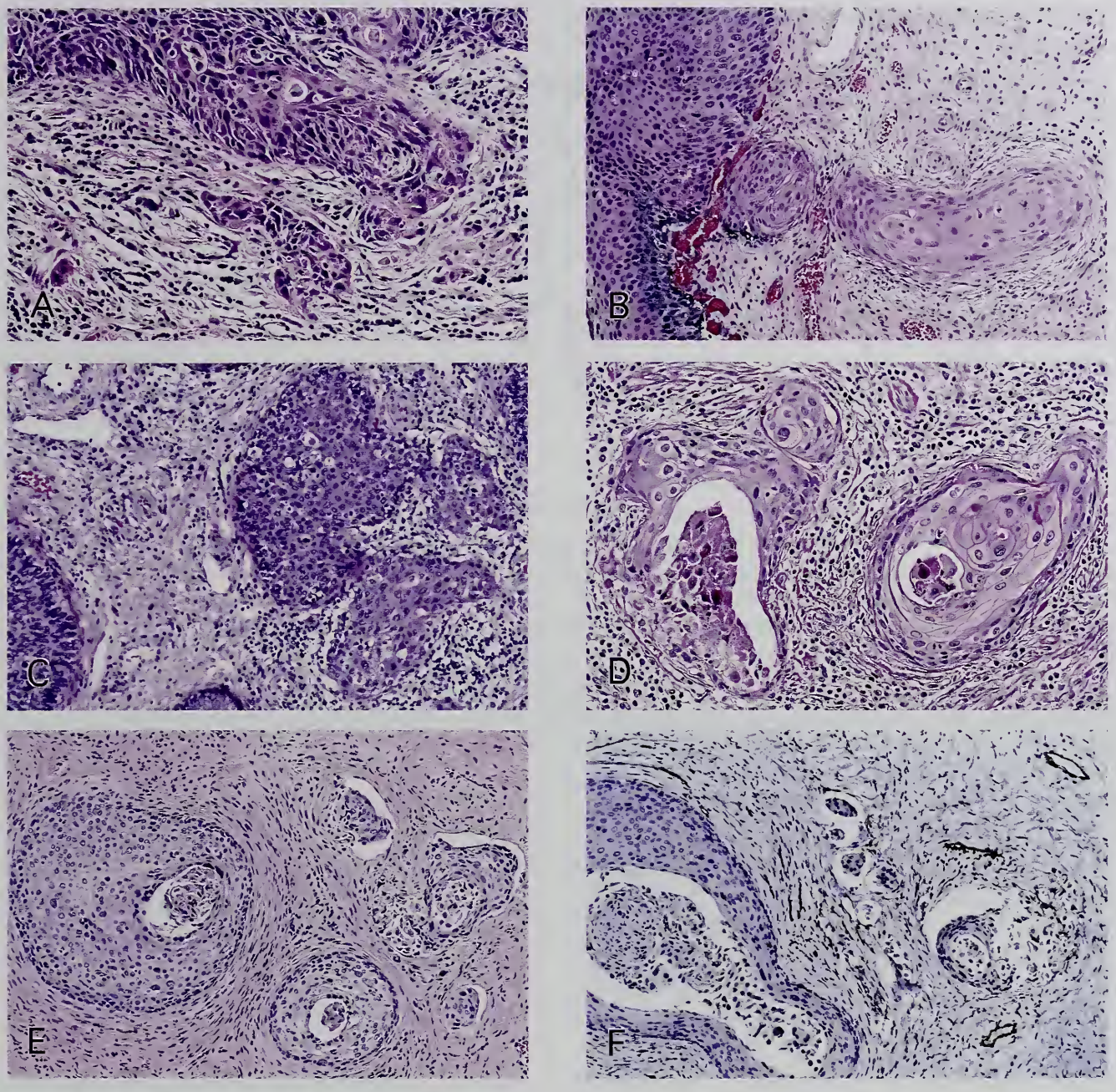


Figure 5-48

MICROINVASIVE SQUAMOUS CELL CARCINOMA

A: One tongue of microinvasive squamous cell carcinoma is attached to overlying HSIL, and one detached island and a small cluster of cells are present in the superficial stroma.

B: A tongue of atypical keratinizing squamous epithelium extends into superficial stroma from overlying HSIL and is surrounded by reactive stroma and an inflammatory infiltrate. The atypical squamous epithelium contains cells with abundant eosinophilic cytoplasm ("paradoxical maturation"). Nuclear chromatin is uniform and vesicular rather than hyperchromatic.

C: Nests of microinvasive carcinoma are surrounded by a reactive, inflamed stroma. The chronic inflammatory cell infiltrate along the epithelial-stromal interface and within the epithelium creates a "moth-eaten" appearance. Nearby, a portion of a basophilic nest of HSIL with peripheral nuclear palisading is present within an endocervical gland.

D: Irregular nests of carcinoma exhibit squamous differentiation, with central necrosis, and are surrounded by reactive, inflamed stroma.

E: Nests of squamous carcinoma within tissue spaces surrounded by clefts suggest vascular invasion.

F: Immunohistochemical stain for CD31 performed on a deeper section from the specimen in figure E shows an absence of vascular endothelium lining the spaces, consistent with tissue retraction artifact simulating vascular invasion.

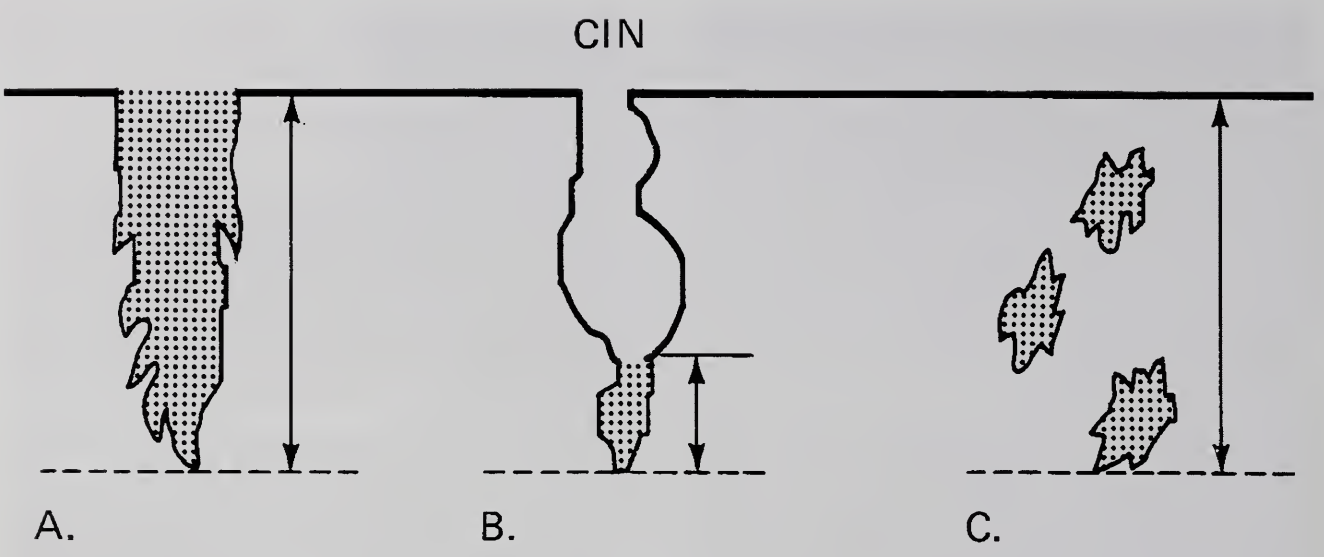


Figure 5-49

METHODS FOR MEASURING DEPTH OF STROMAL INVASION

A: The invasion originates from the surface so depth of invasion is measured from the basal lamina of the surface epithelium to the deepest cell of the invasive focus.

B: The invasion originates from a gland so depth of invasion is measured from the gland (not from the surface) to the deepest cell of the invasive focus.

C: The origin of invasion is indeterminate so invasion is measured from the basal lamina of the surface to the deepest cell in the invasive focus. (Fig. 8.5 from Wright TC, Ferenczy A, Kurman RJ. Carcinoma and other tumors of the cervix. In: Kurman RJ, ed. Blaustein's pathology of the female genital tract, 5th ed. New York: Springer-Verlag; 1987:224.)

carcinoma. The cells in these microinvasive nests exhibit increased amounts of eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli (paradoxical maturation). Necrosis or squamous pearl formation within nests of atypical squamous epithelium suggests that the microinvasion is present or nearby; deeper levels of evaluation may be of value in such cases. Sometimes the interface between the epithelium and stroma of microinvasive carcinoma is effaced ("moth–eaten") as a result of an intense inflammatory reaction.

Prior biopsy with implantation of benign epithelium or HSIL into the underlying regenerating stroma also simulates microinvasion. The atypical epithelium appears as an isolated focus and usually the overlying epithelium is normal.

The most common problem, however, is overdiagnosis of HSIL with gland involvement as microinvasive carcinoma. In a Gynecologic Oncology Group (GOG) study, approximately 50 percent of purported cases of microinvasive carcinoma submitted to a group of reference pathologists were reclassified as HSIL (358).

Treatment and Prognosis. Factors that increase the risk of lymph node metastasis, recurrence, and death include depth of invasion, tumor volume, lymph/vascular space involvement, and status of the cone biopsy resection margins. Lymph node metastasis is uncommon when stromal invasion is 3 mm or less; however, the prevalence of lymph node involvement is 6 percent when invasion is 3.1 to 5.0 mm. Similarly, recurrence or death from cervical cancer almost never occurs when invasion is less than 1 mm, whereas recurrence occurs in approximately 1 percent of patients when tumors invade up to 3 mm and 5 percent when there is 3.1 to 5.0 mm of invasion (80,84,219,363).

Lymph/vascular space involvement occurs in up to 8 percent of microinvasive squamous cell carcinomas that invade less than 1 mm and in 9 to 29 percent of tumors invading 1 to 3 mm (219,358,363). Invasive carcinoma is found in most hysterectomy specimens following cone biopsy in which vascular invasion is identified. Because of this, the prevailing view in the United States is that the presence of lymph/vascular

invasion in minimally invasive carcinomas excludes a diagnosis of microinvasive squamous cell carcinoma.

Studies from Austria have reported no pelvic node metastasis when tumors have a volume of 420 mm^3 or less (56). Determination of volume, however, requires serial sectioning of the cone biopsy specimen, which is labor intensive and costly. As a result, FIGO has used lateral extent of tumor in conjunction with depth of invasion as a surrogate for tumor volume. As the depth of invasion increases, there is an increase in the lateral extent of the carcinoma. In one study, only 6 percent of tumors with 3 mm of invasion or less had greater than 7 mm of horizontal spread compared to 61 percent of tumors with 3 to 5 mm of invasion (394).

Of all of the risk factors, the status of the cone margins is the single most important feature in determining the type of treatment of microinvasive squamous cell carcinoma (84,358). In most studies (237), women whose cone biopsy margins are positive for HSIL or microinvasive carcinoma are much more likely to have residual disease than women whose cone biopsy margins are negative. Moreover, the residual tumors may be deeper than the carcinoma in the cone specimen (237).

The treatment for microinvasive carcinoma has become more conservative in recent years. Treatment is based on the depth of invasion and the presence of vascular invasion. The method for measuring the depth of invasion is shown in figure 5-49. Tumors invading less than 3 mm can be treated by cone biopsy or simple hysterectomy, providing there is no evidence of lymph/vascular invasion. Cone biopsy is considered adequate if the margins are free of disease. A modified (type II) radical hysterectomy is the preferred treatment for superficially invasive carcinoma with lymph/vascular invasion and for tumors invading 3 to 5 mm.

Invasive Squamous Cell Carcinoma

General Features. The incidence and mortality of *invasive squamous cell cervical carcinoma* have decreased dramatically in the United States over the last three decades. The incidence in the United States was 34/100,000 in 1947, 15/100,000 in 1970, and 10 to 12/100,000 in 1986 (97). Although the incidence was decreasing in the United States before the implementation of mass cervical cancer screening programs, screening has had an additional major impact on both the incidence and mortality (65,111). Twenty-one years after the initiation of a mass screening program in Jefferson County, Kentucky, the incidence of cervical cancer decreased by 60 percent, and the mortality in women between the ages of 30 and 59 years decreased by 70 percent. During the same period, there was a 60 percent increase in CIN 3 (65). The significance of cytologic screening in reducing the incidence of cervical cancer is further underscored by comparing the 4.5/100,000 incidence per year in a screened population to the 29/100,000 incidence in an unscreened population (111). Both cohorts exhibited similar epidemiologic characteristics. In the United States, approximately half of the women who develop cervical cancer have not had a cervical smear in the preceding 3 years (156).

According to the most recent global estimates, invasive squamous cell carcinoma is the second most common cancer in women worldwide, with the exception of skin cancer. There are approximately 493,000 new cases of invasive cervical cancer worldwide and 274,000 women die of the disease annually (108). The highest rates are reported in Latin America, where cervical cancer accounts for half of all female cancers. Based on a population-based cancer registry in Panama, the annual incidence of invasive cervical cancer in women between 30 and 50 years of age in high-risk areas is 1/1,000 (333). In developing countries throughout the world, cervical cancer is a major public health problem and is one of the leading causes of death (423). Recent increases in incidence and mortality rates have been observed in some Western countries including Canada, Great Britain, Sweden, and Norway (58,103,215,312). In the United States, there were 12,800 new cases and 4,600 cervical cancer deaths in 2000 (22). The incidence among blacks and Hispanics is two times higher than among whites in the United States. Moreover, in a recent study, after adjusting for a number of demographic factors, age, FIGO stage, other tumor characteristics, and treatment, black women had a higher mortality rate than white women, indicating that race is an independent predictor of cervical cancer survival (170).

Socioeconomic, religious, sexual, obstetric, and dietary factors; immunosuppression; smoking; and oral contraceptive intake have been studied in relation to cervical cancer. Studies suggest that dietary carotenoids and vitamin C have a protective effect against cervical cancer (231,340). The risk of cervical cancer is increased by the number of sexual partners, the age at which sexual intercourse is initiated, and the sexual promiscuity of the male partner. Husbands of women with cervical cancer have more sexual partners than husbands of controls (53). In a recent study, smokers had a two-fold excess risk of cancer, with the risk linked to smoking intensity and duration (51). The effect was most striking among women who had smoked continuously up to the time of cancer diagnosis and women who began smoking late in life, suggesting that smoking played a promotional role in cervical cancer rather than an initiating role. Long-duration use of hormonal contraceptives is associated with an increased risk of cervical cancer but the public health implications depend largely on the extent to which the association remains long after the use of the contraceptives has ceased (380). The role of venereally transmitted agents, particularly HPV, is discussed in chapter 3.

Clinical Features. Invasive squamous cell carcinoma is uncommon before the age of 30 years. Half of the patients, however, are less than 50 years old (372). In the United States, 22 percent of all women with cervical cancer are under the age of 35 years (288) but most are between 45 and 55 years of age at the time of diagnosis. Cervical cancer, however, can occur at almost any age between 17 and 90 years.

The majority of the patients present with intermittent painless vaginal bleeding, often first noted after sexual intercourse or douching. With advancing disease, bleeding may become continuous, and be accompanied by a malodorous discharge and pain. Pain is frequently referred to the flank or leg as a result of tumor invasion of the pelvic wall or sciatic nerve. Involvement of the bladder and rectum during late stages in the evolution of the disease is associated with dysuria, hematuria, rectal bleeding, or obstipation. Involvement of lymphatics may result in edema of the lower extremities.

A cervical biopsy is mandatory for diagnosis. Although sampling problems and incorrect interpretation are partly responsible for false negative smears, necrosis and inflammation on the surface of the tumor may result in only an "atypical smear" that lacks obvious tumor cells. Consequently, the cervix that is abnormal by inspection or palpation is biopsied, even if the cytology smear is normal. In addition to biopsy of the ectocervix, an endocervical curettage is performed as an integral part of the evaluation because invasive carcinoma, particularly adenocarcinoma, frequently involves the endocervical canal and may not be visible on the ectocervix. Clinical tests utilized in the preoperative evaluation of patients with invasive cervical cancer relate to staging and are discussed further in the section on staging.

Cervical cancer is the most common gynecologic cancer to occur during pregnancy: about 3 to 10 percent of cervical cancers occur in pregnant women. In these women, 83 percent present with stage I disease (195).

A number of tumor markers, including carcinoembryonic antigen (CEA), CA125, and a subfraction of the TA-4 antigen called squamous cell carcinoma antigen, are elevated in patients with cervical cancer (203,413). The squamous cell carcinoma antigen appears to have the greatest importance as a serum tumor marker for squamous cell carcinoma because it is elevated in approximately 60 percent of cases and is rarely elevated in cases of adenocarcinoma (100). CEA and CA125 are less commonly elevated. The frequency of elevated levels of CEA is directly related to the stage of disease and has no value in screening (413). Although serum levels of squamous cell carcinoma antigen correlate with the response to treatment, changes in therapy are based on other diagnostic studies, including tissue biopsies, and not on tumor marker levels.

Gross Findings. Squamous cell carcinomas occur either on the ectocervix or in the endocervical canal. They may be exophytic, infiltrative, or ulcerative. Exophytic tumors are polypoid or papillary. When the tumors are large and expand the endocervix, they produce a barrel-shaped cervix. Infiltrative lesions invade the stroma extensively, resulting in very hard lesions with minimal surface change. Ulcerative lesions erode the cervix, resulting an ulcer that involves a portion of the cervix and sometimes the upper vaginal vault.

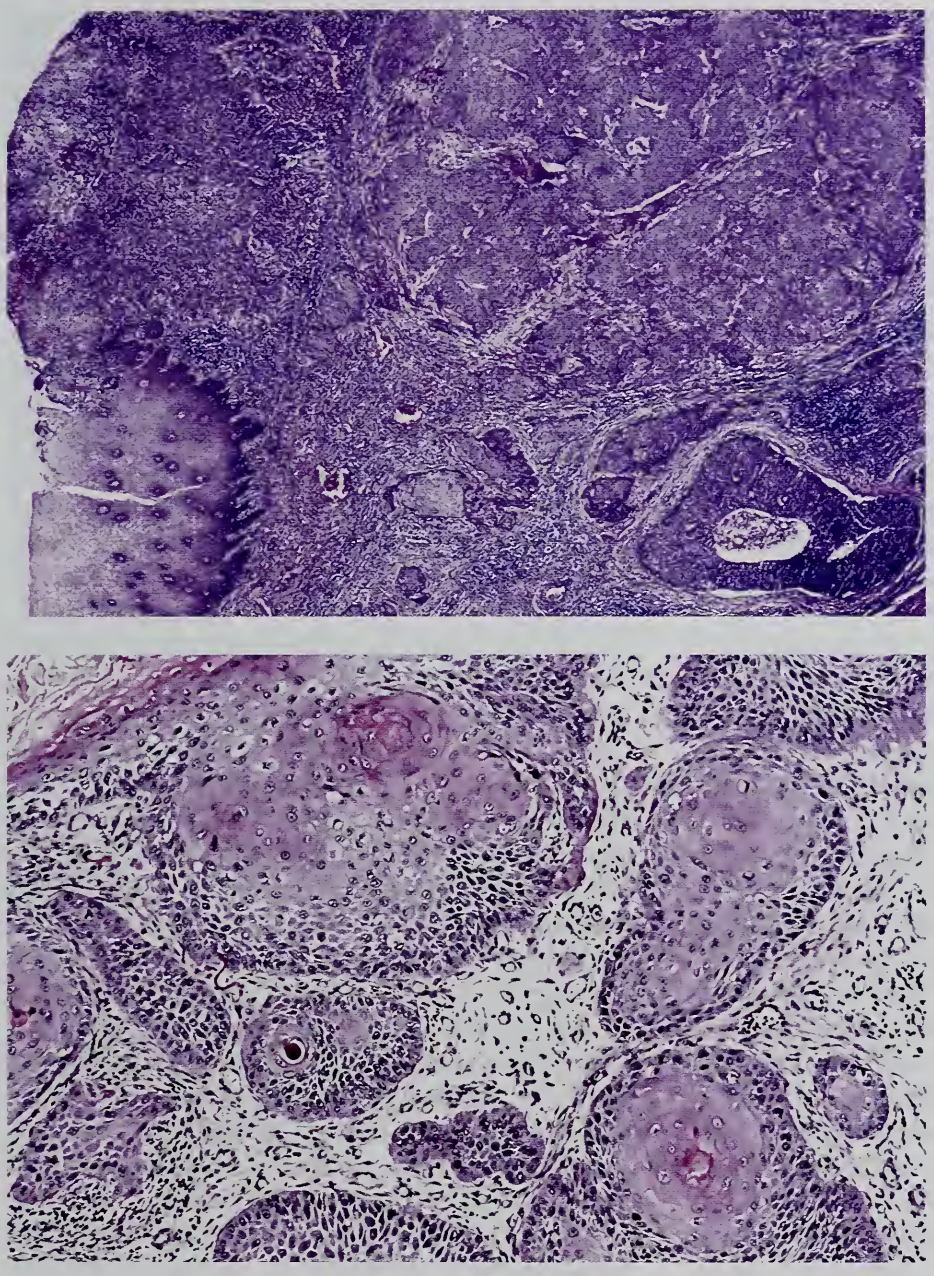


Figure 5-50

INVASIVE SQUAMOUS CELL CARCINOMA

Top: Islands of neoplastic cells invade cervical stroma and replace normal cervical mucosa.

Bottom: Nests of well-differentiated carcinoma exhibit peripheral palisading and central keratinization with squamous pearl formation, reminiscent of the appearance of differentiated normal squamous mucosa.

Microscopic Findings. Invasive squamous cell carcinomas display considerable morphologic heterogeneity, resulting in great variation from one case to another. Most invasive squamous cell carcinomas are composed of compact masses and nests of neoplastic squamous epithelial cells that may show central keratinization or necrosis (fig. 5-50). Other tumors are composed of large masses of squamous cells with little intervening stroma. In still other cases, the neoplastic squamous epithelium invades as cords and individual cells, which may show considerable variation in size, shape, and degree of keratinization. Generally, the cells are oval to polygonal, with eosinophilic cytoplasm. Cell borders are often sharp but may be indistinct, and intercellular bridges are usually not apparent. Nuclei may be relatively uniform or display considerable pleomorphism, and the chromatin tends to be coarse and granular. Mitotic figures are readily apparent, and abnormal mitotic figures are commonly encountered.

Subtypes. Squamous cell carcinomas have been subtyped according to both cell type and degree of differentiation. In the past, the most commonly employed system subdivided squamous cell carcinomas into three categories: large cell nonkeratinizing, large cell keratinizing,

and small cell carcinomas (331). The current WHO classification (see chapter 4) places small cell carcinoma in a separate category and subdivides the remainder into keratinizing and nonkeratinizing squamous cell carcinomas. Nonkeratinizing carcinomas are characterized by rounded nests of neoplastic squamous cells often showing individual cell keratinization. These tumors are distinguished from keratinizing carcinomas by the absence of keratin pearls. The cells are relatively uniform, and the cell borders are indistinct. The nuclei are round to oval and contain coarse chromatin. Mitotic figures are numerous.

Keratinizing carcinomas are characterized by mature squamous cells arranged in irregularly shaped nests or cords that vary considerably in size. The most striking feature is the presence of keratin pearls within the nests of neoplastic squamous epithelium. A keratin pearl is a rounded nest of squamous epithelium in which the cells are arranged in concentric circles surrounding a central focus of acellular keratin. The presence of one pearl is sufficient for a diagnosis of keratinizing squamous cell carcinoma (331). Individual squamous cells are large, with abundant eosinophilic cytoplasm, and many show individual cell keratinization. The cells are closely apposed and often have prominent intercellular bridges. The nuclei may be enlarged or pyknotic. Mitotic activity is relatively low compared with the other tumor types.

Some squamous cell carcinomas are composed of small oval-shaped basaloid cells with scant cytoplasm growing in masses and nests (4). The nuclei are hyperchromatic and display abundant mitotic activity. Necrosis is frequently observed. Foci of more obvious squamous differentiation and keratinization are sometimes present, but keratin pearls are absent. These are similar to tumors occurring in the vagina and vulva, which have been designated basaloid carcinoma. Squamous cell carcinomas composed of small cells should be distinguished from small cell undifferentiated or oat cell-like carcinoma.

There is considerable potential for confusion when the term small cell carcinoma is used to describe a small cell nonkeratinizing squamous cell carcinoma in contrast to a small cell undifferentiated carcinoma similar to the oat cell carcinoma of the lung. It is therefore recommended that the term small cell carcinoma be reserved for tumors resembling small cell, i.e., neuroendocrine, tumors in other anatomic sites such as the lung. Most studies have concluded that distinguishing keratinizing and nonkeratinizing squamous cell carcinomas provides no useful prognostic or therapeutic information (137,149). In our opinion, it is not necessary to include this information in the surgical pathology report.

Microscopic Grading. Most pathologists grade squamous cell carcinomas of the cervix into well, moderately, or poorly differentiated lesions. Well-differentiated tumors (grade 1) are composed predominantly of mature squamous cells, with abundant keratin and pearl formation and minimal mitotic activity. The nuclei are uniform and the cells occasionally display well-developed intercellular bridges. Moderately differentiated carcinomas (grade 2) are composed of cells with less abundant cytoplasm. Cell borders are less distinct, and the nuclei have greater pleomorphism (fig. 5-51). Mitotic activity is higher than in well-differentiated tumors. Poorly differentiated neoplasms (grade 3) are composed of masses and nests of small, primitive-appearing oval cells with scant cytoplasm and hyperchromatic spindle-shaped nuclei with high mitotic activity. Keratinization is minimal or absent. Pleomorphic carcinomas that have minimal squamous differentiation, bizarre highly pleomorphic nuclei, and abundant mitotic activity are also included in this category.

Most recent studies have failed to show that this grading system correlates with outcome (85,86,447). A study from the GOG evaluated a number of different grading systems, including those proposed by Zaino et al. (447), in surgically treated stage IB patients as well as nuclear grade, degree of keratinization, mitotic activity, pattern of infiltration, and degree of lymphoid response. None of these parameters had prognostic significance.

In an effort to improve the predictive value of histologic grading and to identify high-risk patients who might benefit from more aggressive therapy at the outset, a "malignancy grading system" has been described (8,387). This system evaluates eight parameters: structure, cell type, nuclear atypia, mitotic activity, type of tumor margin, pattern of invasion, vascular

invasion, and inflammatory reaction to assess the tumor-host relationship more completely. Using the malignancy grading system and an abbreviated version, some investigators have reported that this system was superior to staging in predicting prognosis (41,386). Other groups have been unable to confirm these findings (86,209). Currently, the malignancy grading system is not used in clinical practice.

There has been no conclusive demonstration that a histologic grading system or the histologic typing system proposed by Reagan et al. (331) reliably predicts prognosis. Zaino et al. (447) found, however, that the presence of vascular invasion and depth of invasion were highly reliable predictors of behavior. Accordingly, in reporting squamous cell carcinomas, the depth of invasion (in millimeters or the proportion of the wall invaded), the presence or absence of vascular invasion, and the size of the tumor (greatest tumor dimension) should be reported. Histologic grading and classification into keratinizing and nonkeratinizing types are optional.

Cytologic Findings. Keratinizing squamous cell carcinoma is characterized by caudate and spindle cells with marked variation in size and shape, having dense orangeophilic cytoplasm. Nuclei are variable in size and have irregular membranes, with coarsely granular, irregularly distributed chromatin (fig. 5-52). Nonkeratinizing squamous cell carcinoma is characterized by single cells or syncytial aggregates of cells having a high nuclear-cytoplasmic ratio, nuclear pleomorphism, and irregularly distributed coarsely clumped chromatin. In some large cell types, the cells have moderate amounts of cytoplasm and nuclei are more vesicular with prominent nucleoli (287).

Immunohistochemical Findings. Squamous cell carcinomas of the cervix express a variety of keratins that differ in pattern and number depending on the degree of differentiation (378). Differentiated keratinizing carcinomas have the most complex pattern of intermediate keratin filaments, which resemble those characteristic of terminally differentiated cervical keratinocytes including CK4, 5, 6, 8, 13, 14, 16, 17, 18, and 19. Nonkeratinizing squamous carcinomas always express CK6, 14, 17, and 19 and in some cases 4, 5, 7, 8, 10, 13, 16, and 18. Although these findings may in the future provide some insight into the pathogenesis of cervical carcinoma, they have thus far not been shown to assist in histologic diagnosis.

CEA and the cervical carcinoma tumor-associated antigen, TA-4, can be localized immunohistochemically in squamous cell carcinomas, but as with the cytokeratins, are not routinely used in clinical practice. The *ras* oncogene product p21 can be localized at the cell membrane of invasive squamous cell carcinoma by immunohistochemical methods on formalin-fixed, paraffin-embedded tissue. Overexpression of p21 in large cell keratinizing and nonkeratinizing squamous cell carcinomas is associated with a poor prognosis (346).

Virtually all invasive squamous carcinomas express p16 (fig. 5-51E). As with HSIL, diffuse, moderate to strong expression is related to the presence of high-risk HPV. In addition, squamous carcinomas have significantly increased proliferative activity as assessed by immunohistochemical expression of Ki-67 (fig. 5-51F).

It has been reported that p63 (422), a member of the *p53* gene family, is preferentially expressed, almost exclusively, in the nucleus of basal cells and immature squamous epithelium. p63 is strongly homologous to p53 in sequence and function, and encodes for at least six protein isoforms, with or without a transactivation (TA) domain. The TA isoforms show a p53-like tumor suppressor function whereas those isoforms without a TA domain appear to exert an oncogenic effect. Strong and diffuse immunopositivity for p63 was detected in 97 percent of squamous cell carcinomas but not in invasive adenocarcinomas (422). p63 was absent or only minimally expressed (less than 30 percent of cells) in neuroendocrine carcinomas (422). Thus, immunostaining for p63 can be useful in the differential diagnosis of squamous, glandular, and neuroendocrine tumors of the cervix.

Morphometric Findings. Using flow cytometry, 33 to 80 percent of squamous cell carcinomas are aneuploid (181). Although there is some disagreement, most flow cytometry studies have failed to demonstrate an independent significant effect on clinical outcome (181,184). Tumors that are "diploid" have chromosomal alterations and are therefore actually aneuploid but at a level too low to be detected by flow cytometry.

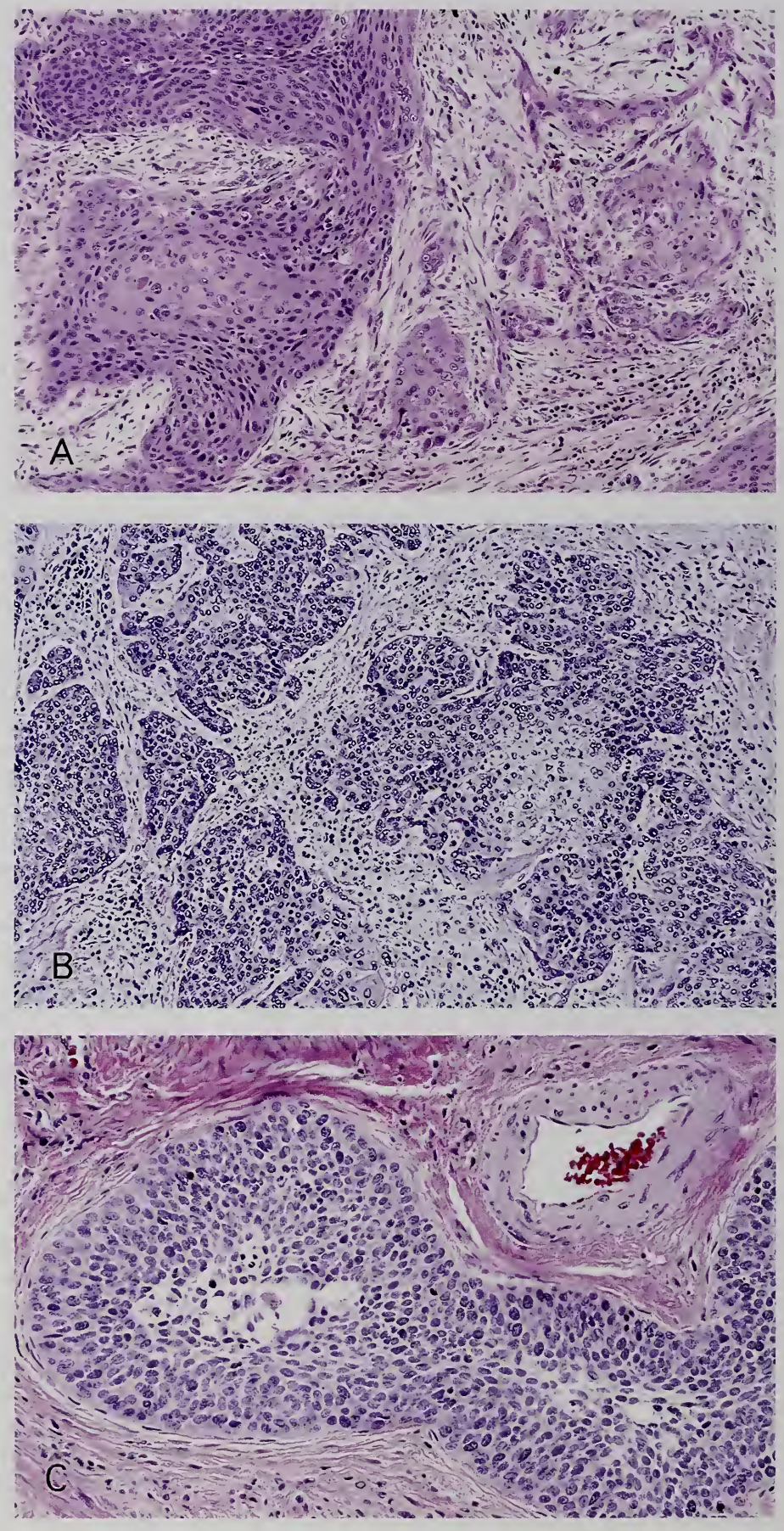


Figure 5-51

INVASIVE SQUAMOUS CELL CARCINOMA

A: Moderately differentiated carcinoma is characterized by cells that retain moderate amounts of eosinophilic cytoplasm. Markedly irregular tumor nests infiltrate inflamed desmoplastic stroma.

B: Moderately to poorly differentiated carcinoma is composed of nests of tumor cells with predominantly basaloid differentiation. Focal cytoplasmic clearing within the squamous epithelium (clear cell change) can simulate clear cell carcinoma when extensive.

C: Pure basaloid squamous carcinoma simulates HSIL but is present deep in the cervical stroma adjacent to a large vessel.

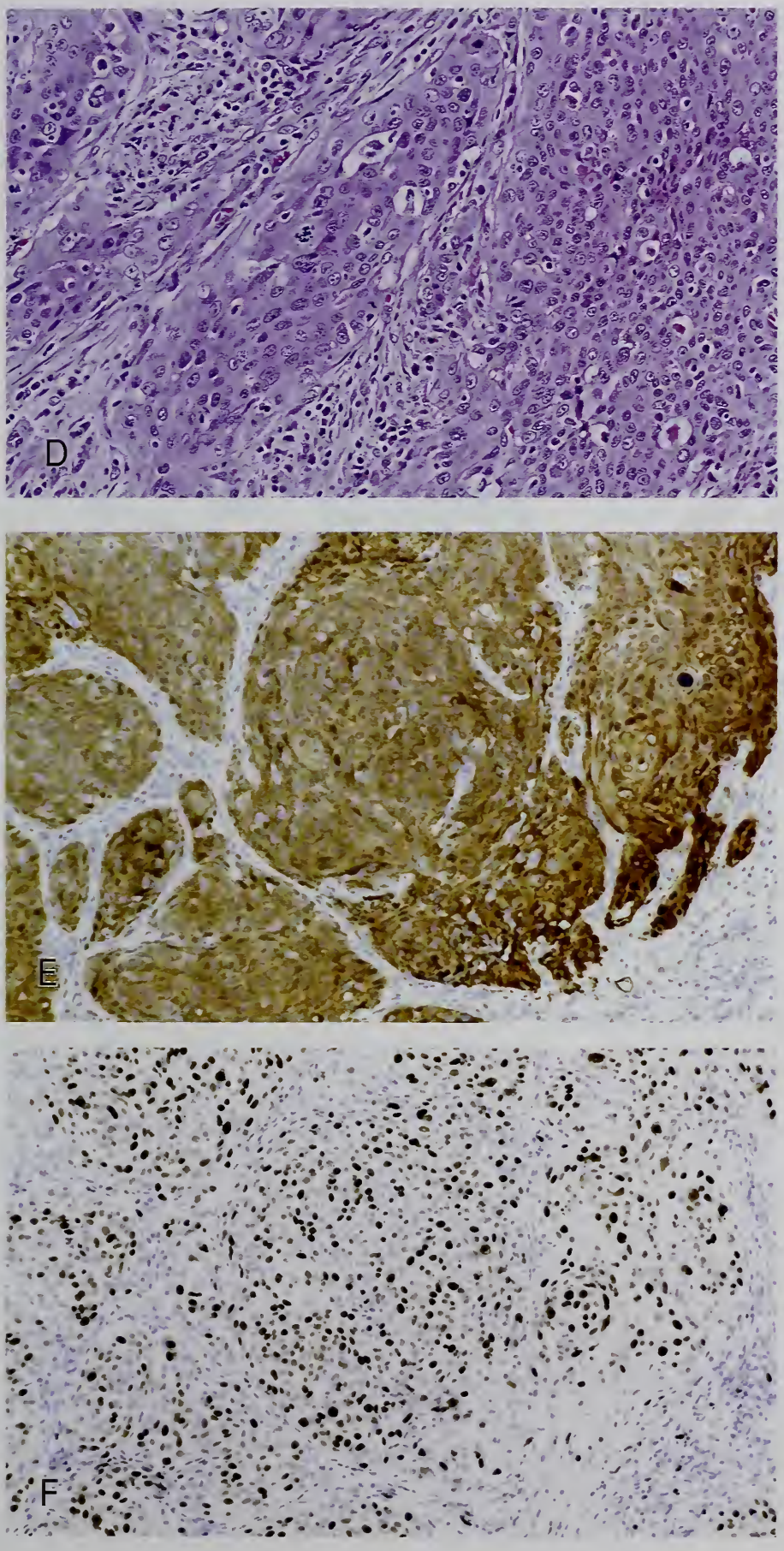


Figure 5-51 (Continued)

D: Poorly differentiated carcinoma is composed of atypical cells with moderate amounts of eosinophilic cytoplasm but limited keratinization.

E: The tumor exhibits diffuse, strong expression of p16, which correlates with the presence of high-risk HPV.

F: The tumor has a very high Ki-67 proliferation index.

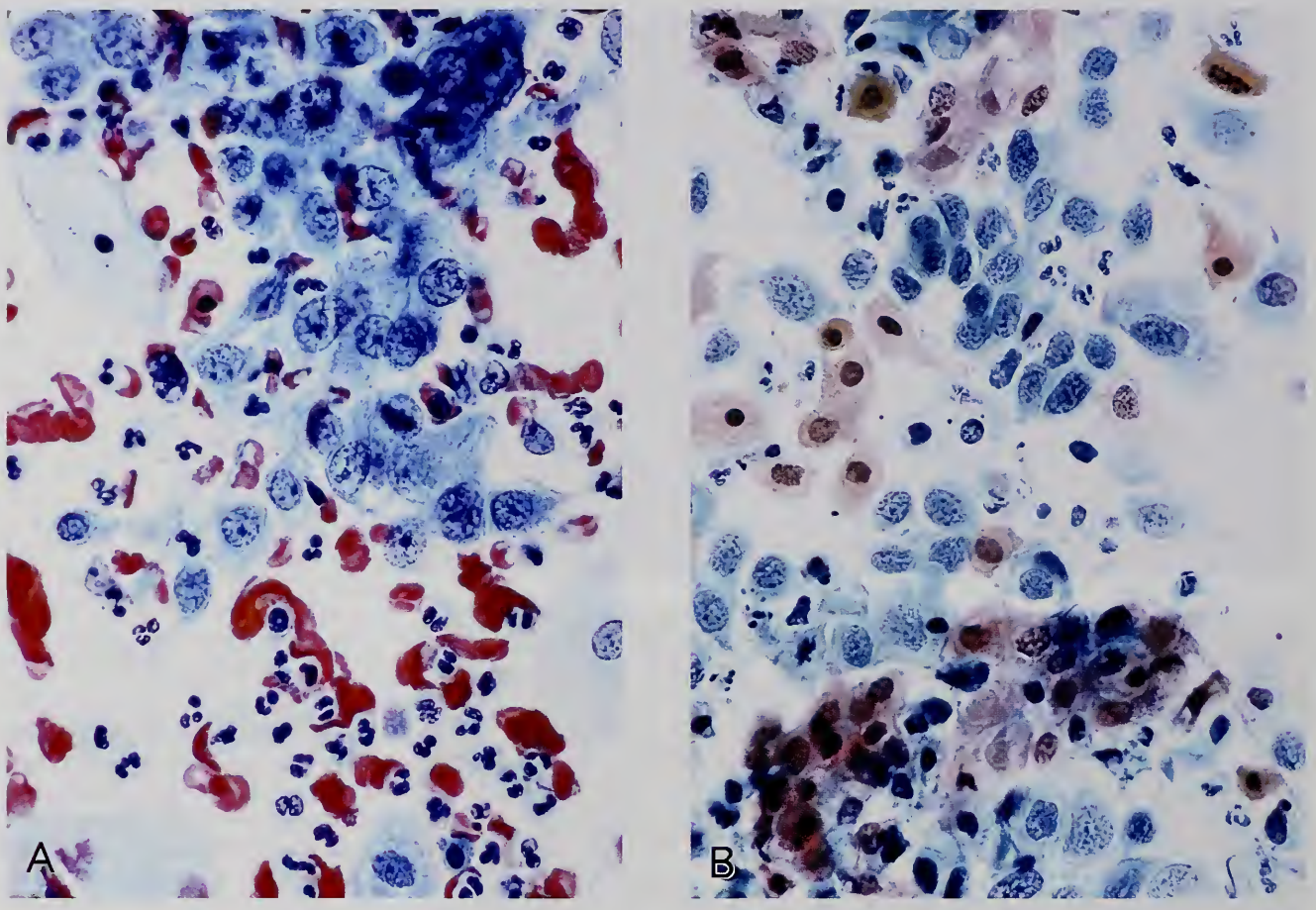


Figure 5-52

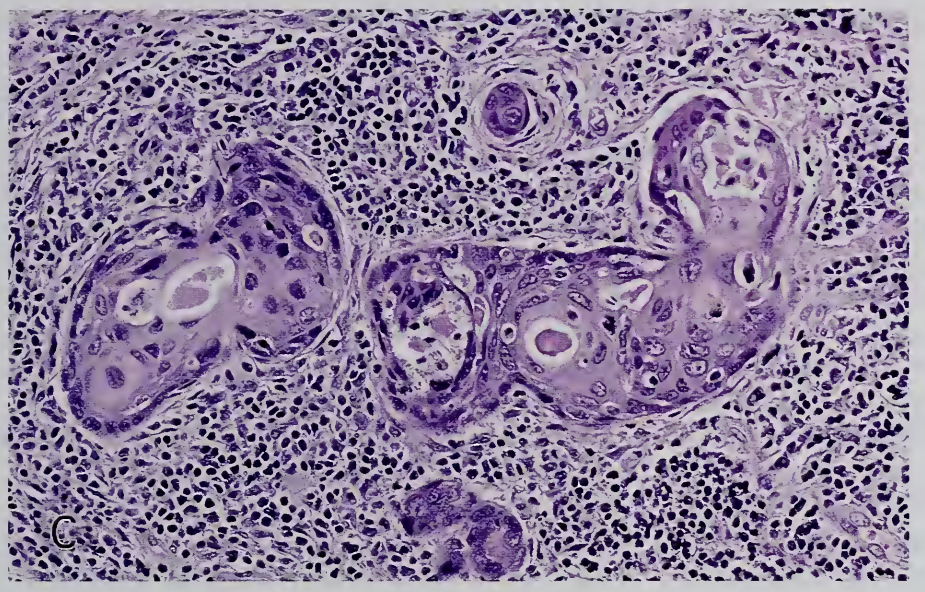
INVASIVE SQUAMOUS CELL CARCINOMA

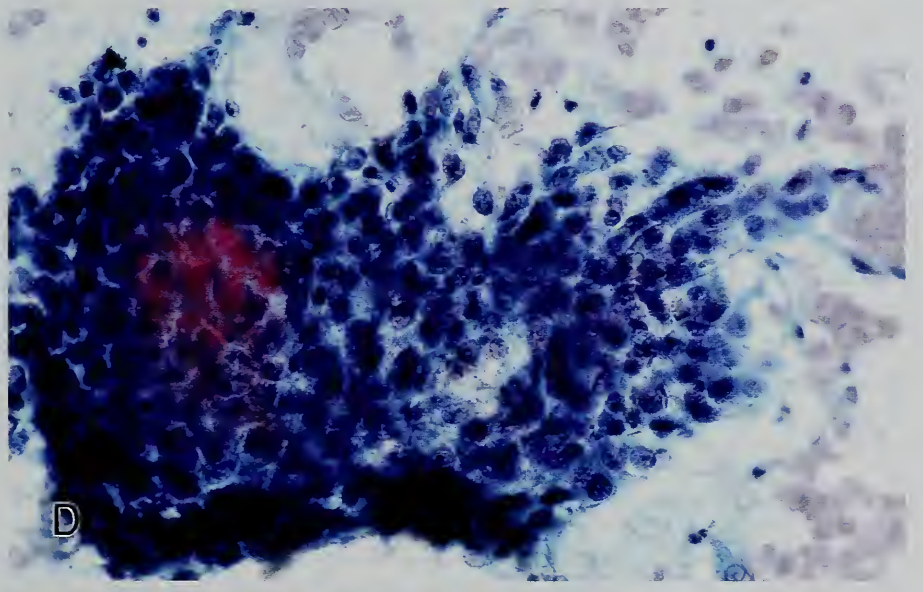
A: Cytologic preparation shows cells with moderate to abundant cytoplasm and enlarged, atypical vesicular nuclei with prominent nucleoli.

B: Cytologic preparation demonstrates markedly atypical keratinizing and nonkeratinizing squamous cells.

Molecular Genetic Findings. Currently, there is little consensus on the prognostic implications of alterations in the genes of cervical cancer. Specific point mutations of the first exon of *ras* genes as well as amplification and loss of heterozygosity of *ras* genes occur in a high proportion of cervical carcinomas. Overexpression of the *ras* gene product p21 is associated with a poor prognosis (346). Amplification of the *c-myc* oncogene is associated with advanced stage disease and overexpression of *c-myc* is associated with a poor prognosis in some studies but not in others (335,336). HPV typing, while initially thought to be prognostic, is probably not an independent diagnostic factor. All of these molecular genetic studies are small and the findings preliminary. At present, they play no role in clinical diagnosis or management.

Differential Diagnosis. Invasive squamous cell carcinoma can be confused with benign lesions, including squamous metaplasia with extensive gland involvement and a marked decidual reaction. The features that distinguish these lesions from carcinoma are the absence of nuclear atypia and the level of mitotic activity. Although immature squamous metaplasia may display a low level of mitotic activity, the cells are uniform in size and shape, and lack significant nuclear atypia. Immunohistochemistry using an antibody against p16 can help in this situation since p16 is expressed by virtually all cervical squamous cell carcinomas but not in immature metaplasia. Decidual cells can sometimes be confused with squamous cells carcinoma cells. Decidual cells lack mitotic activity and display no cytologic atypia.





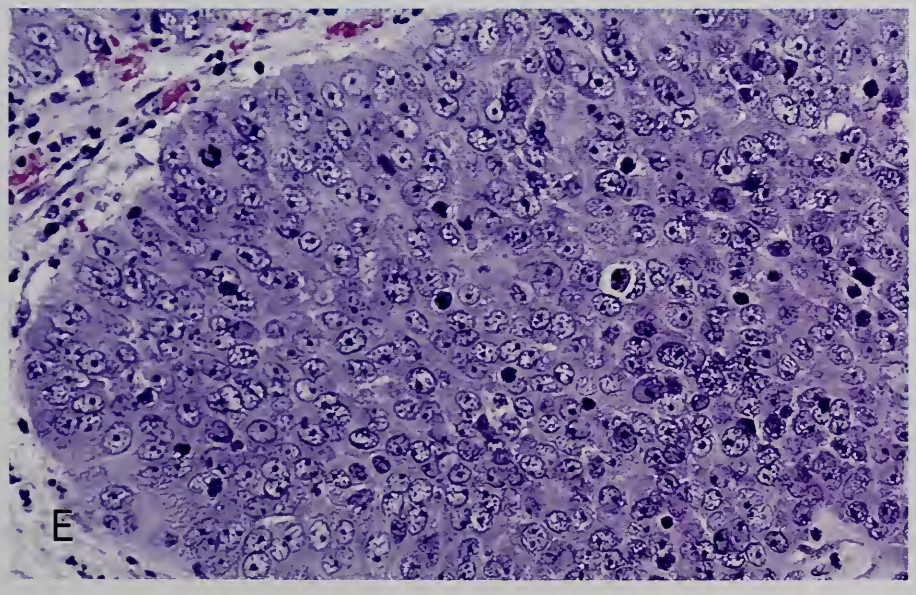


Figure 5-52 (Continued)

C: Tissue specimen corresponding to the cytologic specimen in B shows irregular nests of invasive keratinizing squamous cell carcinoma.

D: Cytologic preparation demonstrates a densely cellular sheet of nonkeratinizing, markedly atypical squamous cells.

E: Tissue specimen corresponding to the cytologic specimen in D shows poorly differentiated nonkeratinizing squamous cell carcinoma.

Immunoperoxidase reactions for cytokeratin are negative in decidual cells but strongly positive in carcinoma cells.

Placental-site nodules may also be confused with squamous cell carcinoma (438). Typically, the trophoblastic cells in placental site nodules are arranged in nests surrounded by hyaline material and show no or minimal mitotic activity. Placental site nodules are positive for Mel-CAM (CD146) and inhibin, and focally positive for placental lactogen. In contrast, squamous cell carcinomas are not well circumscribed, show at least some mitotic activity, and are not positive for CD146, inhibin, and placental lactogen.

Rarely, epithelioid trophoblastic tumors (ETTs) occur in the cervix and may be confused with hyalinizing squamous cell carcinomas. In contrast to squamous cell carcinomas, ETTs express CK18 and inhibin. Conversely, squamous cell carcinomas are strongly and diffusely positive for p16, whereas ETTs are negative (366–368).

There may be confusion with clear cell carcinoma when squamous cell carcinoma contains cells with abundant glycogen, resulting in masses of clear cells that resemble the solid areas of clear cell adenocarcinoma. In addition to the solid areas, clear cell adenocarcinoma almost always has papillary or tubulocystic areas and hobnail as well as clear cells. Clear cell adenocarcinoma also lacks squamous differentiation.

Poorly differentiated squamous cell carcinoma that is composed predominantly of small cells can be difficult to distinguish from small cell (undifferentiated) carcinoma of neuroendocrine type (see Other Epithelial Tumors - Small Cell Carcinoma). Neurosecretory granules, evident by immunohistochemical staining or electron microscopy, are typically identified in small cell (undifferentiated) carcinoma. Occasionally, however, both methods are negative for dense-core granules. Conversely, some small cell carcinomas have squamous cell features on electron microscopy. In most cases, small cell carcinoma can be distinguished from a squamous cell carcinoma composed of small cells on the basis of conventional light microscopic features. Small cell carcinomas have a distinctive growth pattern characterized by diffuse infiltration by small nests, sheets, and, typically, individual cells. Rosettes, trabeculae, and ribbons are also frequently present. Squamous cells are larger, with larger nuclei and abundant cytoplasm. The nuclei lack prominent nucleoli and are intensely hyperchromatic, with smudged chromatin that obscures the nuclear detail. A characteristic crush artifact is another useful diagnostic clue that occurs in small cell carcinoma. The small cells of squamous cell carcinoma have oval-shaped nuclei and granular chromatin arranged in cohesive nests. Squamous differentiation is occasionally seen in the center of some nests. The cells in these nests tend to be perpendicular to the basement membrane (143). The distinction may be extremely difficult; in these cases, immunohistochemistry and electron microscopy may be helpful.

Spread and Metastasis. Cervical carcinoma spreads primarily by local extension and lymphatic spread; hematogenous spread is unusual. Local extension may involve the adjacent vaginal mucosa, parametrial soft tissue and pelvic wall, lower uterine segment and corpus, and hypogastric, external iliac, and sacral lymph nodes; secondarily, the common iliac, inguinal, and paraaortic nodes are involved (163). There is a close correlation between the stage of the tumor and the frequency of lymph node metastasis. Lymph node involvement occurs in 15 to 20 percent of stage IB tumors, 25 to 40 percent of stage II tumors, and 50 percent of stage III and IV tumors. Approximately one third of patients with paraaortic lymph node involvement have metastases to the scalene nodes.

Staging. The current FIGO and TNM staging systems are shown in Tables 5-1 and 5-2. Clinical staging primarily permits comparison of the results of treatment and provides guidelines for therapy. The stage approximates the extent of disease. Chest X ray, intravenous pyelography, cystoscopy, proctosigmoidoscopy, and barium enema are performed routinely to determine the stage. Lymphangiography, ultrasound, and computerized tomography (CT) scanning are not used for clinical staging. Surgical staging is used to determine the presence of extrapelvic disease. Careful surgical staging reveals that the clinical stage is often inaccurate, with error rates ranging from 25 percent in stage I cases to 50 percent in stage III cases (372). These discrepancies explain why the clinical stage is a relatively insensitive predictor of outcome.

Treatment. The treatment of frankly invasive squamous cell carcinoma is determined primarily

by the clinical stage. Advanced stage disease, i.e., beyond stage IIA, is treated primarily by radiotherapy or a combination of radiation and chemotherapy, whereas early stage disease is treated by either radiation or a radical surgical procedure. A combination of radiation and extrafascial hysterectomy is performed for large-volume and barrel-shaped lesions because the upper limits of the tumor extend beyond the range of the radiation field. Survival of stage IB patients treated by either radical surgery or radiation is 80 to 85 percent. Surgery is preferred for younger women because the ovaries can be conserved and there is less likelihood of sexual dysfunction as there is after radiation. Radical surgery is not performed if extrapelvic disease is discovered at the time of the operation. The radical surgery performed for stages IB and IIA disease consists of a hysterectomy and wide excision of parametrial and paravaginal tissue. Upper vaginectomy and pelvic lymphadenectomy are also performed.

Recent studies have shown that regimens of radiotherapy and chemotherapy that contain cisplatin improve the rates of survival and progression-free survival among women with locally advanced cervical cancer (342). A combined regimen of radiotherapy and chemotherapy using cisplatin was shown to reduce the risk of recurrence and death in women with bulky stage IB tumors (208).

Prognosis. The prognosis after surgical treatment for patients with stage IB squamous cell carcinoma depends on a variety of interrelated factors, the most important of which, in order of importance, are depth of invasion, tumor size, lymph-vascular space involvement (LVSI), lymph node status, tumor volume, and clinical stage (362). Using a multivariate survival tree analysis, based on the depth of invasion (DI) in mm, LVSI (positive or negative), lymph node metastasis, and age, Sevin et al. (362) were able to assign an individual patient to one of three risk groups. The 5-year disease free survival (DFS) rate for these three groups was 91 percent, 68 percent, and 43 percent. Patients with microinvasive carcinoma and small cell carcinoma were not included in this analysis. According to this study, these four parameters are all that is required to determine prognosis for patients with stages I and II squamous carcinoma. Patients with tumors of DI equal to or less than 6 mm had a DFS rate of 92 percent compared to 64 percent for women with tumors of DI greater than 6 mm. In patients with tumor DI up to 6 mm, LVSI is not an important risk factor, whereas in patients with tumors in which DI was 7 to 22 mm, LVSI is the most significant variable affecting DFS. Similarly, lymph node metastasis is an important risk factor only in patients with tumor DI of 7 to 20 mm.

Most recurrences occur within 2 years of treatment, and 85 percent of patients who die of disease do so within 3 years (99). In view of the cellular changes induced by radiation, a diagnosis of carcinoma based on cytologic findings may be difficult. A diagnosis of recurrent disease should be based on a histologic diagnosis, which permits evaluation of architectural and cytologic features. Nearly 75 percent of recurrences occur in the pelvis; of the remainder, approximately 6 percent involve the lungs (172). Ureteral obstruction with subsequent development of uremia is a complication of recurrent cervical carcinoma in 40 percent of patients (205). After recurrence, the 1-year survival rate is 10 to 15 percent. Recurrent disease that is confined to the upper vagina and parametrial area can be treated by pelvic exenteration, but with current sophisticated radiotherapy, isolated central pelvic recurrence is rare. Recurrent disease is almost always treated palliatively.

Verrucous Carcinoma

Verrucous carcinoma is a distinctive type of very well-differentiated squamous cell carcinoma that characteristically tends to recur locally but does not metastasize (228). Because of the problems in diagnosis and the confusion in terminology, it is difficult to be certain how many authentic cases of verrucous carcinoma of the cervix have been reported, but it is probably around 20 to 30 (87). In the past, this tumor was termed by some "giant condyloma of Buschke-Lowenstein," but the implication that this tumor is a type of condyloma is erroneous and confusing and therefore it is no longer used. Because verrucous carcinomas are more common on the vulva, they are described in detail in chapter 7.

Although HPV type 6 (302) and an unusual variant designated 6b (330) have been identified within verrucous carcinomas of the vagina and

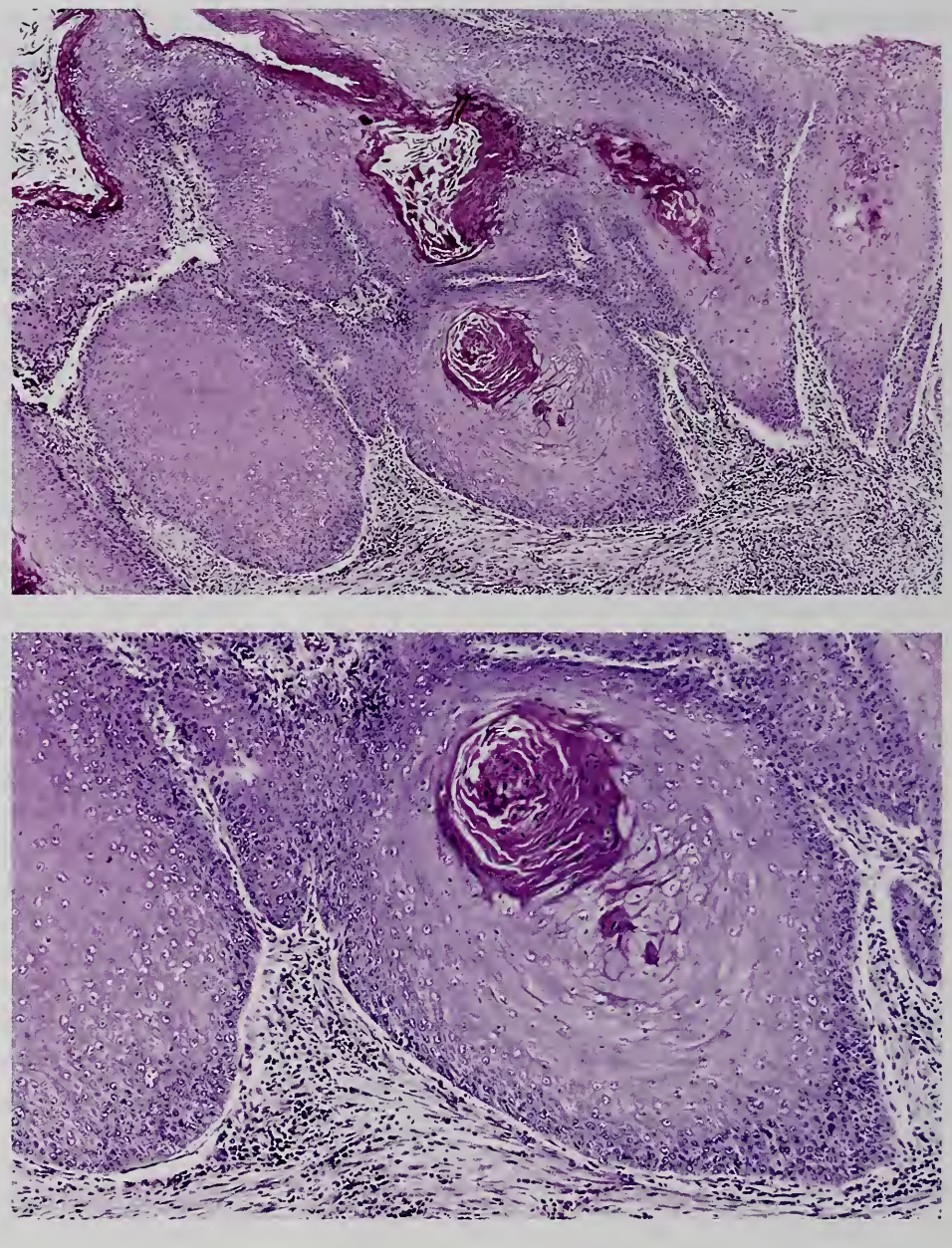


Figure 5-53

VERRUCOUS CARCINOMA

Top: Well-differentiated keratinizing verruciform epithelium has broad smooth nests at the base of the tumor.

Bottom: The tumor exhibits minimal atypia. Basal nests have a smooth interface, invading with a pushing border into the adjacent desmoplastic stroma.

vulva by polymerase chain reaction (PCR), a recent study failed to detect HPV DNA in the tumors and suggested that verrucous carcinomas may not be HPV related (284). Clinically, verrucous carcinoma is a slow-growing, locally invasive neoplasm that occasionally pursues a relentless course manifested by uncontrolled local recurrence that ultimately results in the death of the patient.

On gross examination, verrucous carcinomas have a warty, fungating appearance. Typically, the tumors are large and bulky and occasionally ulcerated. On cut section, the deep margin is characteristically sharply circumscribed.

Microscopically, verrucous carcinomas are exophytic, with an undulating hyperkeratinized surface composed of rounded or pointed papillary projections that lack central fibrovascular cores. The lack of fibrovascular cores is particularly useful in distinguishing a verrucous carcinoma from a condyloma acuminatum, which displays prominent fibrovascular cores. The deep margin of a verrucous carcinoma is composed of large bulbous masses that invade along a wide front in a "pushing" fashion (fig. 5-53). Laminated keratin whorls are present within the masses of epithelium. The typical features of the usual form of invasive squamous carcinoma, irregular prongs and small nests of neoplastic squamous cells infiltrating the stroma, are absent unless a squamous cell carcinoma

has supervened. The neoplastic squamous cells show almost no nuclear atypia. At most, the nuclei are slightly enlarged and may show slight coarsening of the chromatin with some prominent nucleoli. Mitotic activity is usually low, and koilocytosis is not present.

A benign condyloma may enlarge dramatically, particularly during pregnancy, and regress spontaneously. Such a neoplasm should be classified as a condyloma acuminatum, without the adjective giant, to avoid confusion with verrucous carcinoma. Squamous cell carcinoma may arise in a condyloma, but this tumor is also not synonymous with verrucous carcinoma. Such a lesion should be classified as well-differentiated invasive squamous carcinoma arising in a condyloma acuminatum. Squamous cell carcinoma may also arise immediately adjacent to a verrucous carcinoma and merge with it. Such a tumor should be termed a mixed verrucous and invasive squamous cell carcinoma.

Warty (Condylomatous) Carcinoma

Warty (condylomatous) carcinoma is a squamous cell carcinoma that has a condylomatous or warty appearance on microscopic examination. Although these tumors can develop in the cervix and vagina, they are more common in the vulva (250).

Like verrucous carcinoma, warty carcinoma is a less aggressive tumor than typical well-differentiated squamous cell carcinoma, although the experience with this tumor is extremely limited. Warty carcinoma, unlike verrucous carcinoma, has an irregular infiltrating margin similar to the usual type of invasive squamous cell carcinoma. The feature that sets warty carcinoma apart from the usual type of squamous carcinoma and from verrucous carcinoma is the presence of numerous enlarged cells with enlarged, highly pleomorphic nuclei that have a distinct "viral type" appearance, which strongly resembles the koilocytotic atypia of LSILs of the cervix. Warty carcinomas of cervix and vagina, unlike those on the vulva, do not appear to have a distinctive virologic or clinical profile (see chapters 6 and 7).

Papillary Squamous Cell (Squamotransitional) Carcinoma

Papillary squamous cell (squamotransitional) carcinoma is an uncommon neoplasm that resembles papillary transitional cell carcinoma of the urinary bladder and that may display squamous or, rarely, glandular differentiation (328). The largest study of these tumors, reported from the Armed Forces Institute of Pathology (218), consisted of 32 cases. The investigators subdivided the tumors into three groups: 1) predominantly squamous, 2) predominantly transitional, and 3) mixed squamous and transitional. Recently, three cases of papillary transitional cell carcinoma admixed with endometrioid type adenocarcinoma were reported (338) and therefore a fourth group, mixed glandular and transitional, can be added to the classification.

Although these tumors morphologically resemble transitional cell carcinomas of the urinary bladder, all of the four subtypes have the same cytokeratin immunoprofile, which differs from that of bladder tumors. In the cervix, these neoplasms are CK7 positive and CK20 negative whereas in the bladder they are characteristically CK7 and CK20 positive. These findings suggest that the cervix papillary transitional cell tumors are of müllerian origin. Interestingly, HPV 16 has been detected in three papillary squamous cell carcinomas of the cervix (50).

The microscopic appearance of the tumor depends on whether it is predominantly transitional or squamous. To qualify for the diagnosis of papillary squamous (transitional) carcinoma, the tumor should display a papillary architecture with papillae that are covered by several layers of atypical basaloid cells displaying abundant mitoses and little or no evidence of maturation (fig. 5-54). In essence, the cells have the appearance of an HSIL, with hyperchromatic nuclei and scant cytoplasm, closely resembling transitional cell carcinoma of the urinary bladder. If there is no invasion of the underlying cervical stroma, the tumor qualifies as an in situ neoplasm. Invasive squamous carcinoma is usually evident at the base of the tumor but in tumors with broad papillae, invasion may also be detected within the fibrovascular core of the papillae. Sometimes invasion is manifested by well-circumscribed nests of epithelial cells in continuity with papillae extending deep into the stroma. In other areas, the invasive tumor resembles a typical (nonpapillary) squamous cell carcinoma. A superficial biopsy revealing a papillary squamous cell carcinoma must be considered an invasive

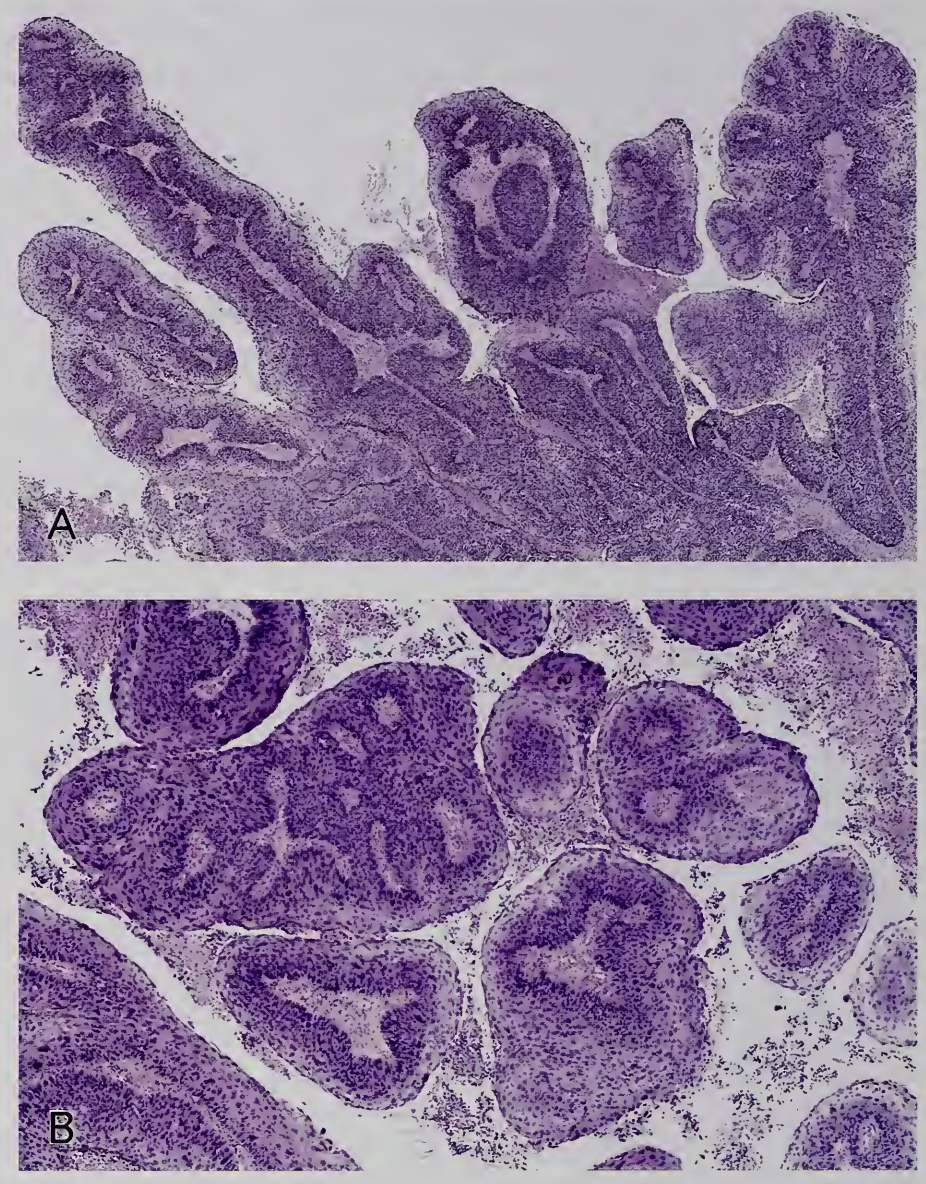


Figure 5-54

PAPILLARY SQUAMOUS CELL CARCINOMA

A: Exophytic tumor forms papillae with fibrovascular cores.

B: Papillae of varying sizes resemble a condyloma at low magnification.

neoplasm until proven otherwise. At minimum, this requires a cone biopsy.

It is important to recognize this entity because it is aggressive and capable of metastasis. It should, therefore, not be confused with a squamous papilloma, inverted transitional cell papilloma, condyloma acuminatum, or verrucous carcinoma. Unlike a squamous papilloma or an inverted papilloma, transitional cell carcinoma is more cellular, displays cytologic atypia, and shows mitotic activity. The same is true for the distinction from a condyloma. In addition, condylomas show evidence of maturation and koilocytosis. Unlike verrucous carcinoma, the projections of papillary squamous cell (transitional) carcinoma are covered by basaloid type cells with hyperchromatic atypical nuclei rather than relatively bland epithelium.

The clinical behavior of papillary squamous cell (squamotransitional) carcinoma resembles that of typical invasive squamous cell carcinoma of the cervix. An exception was the small series reported by Randall et al. (328) in which three tumors recurred after 7 years. This is unusual for squamous cell carcinoma of the cervix.

Lymphoepithelioma-Like Carcinoma

Lymphoepithelioma-like carcinoma is a distinct subset of squamous cell carcinoma that tends to be well circumscribed and is composed of undifferentiated cells surrounded by a marked inflammatory infiltrate in the stroma (162).

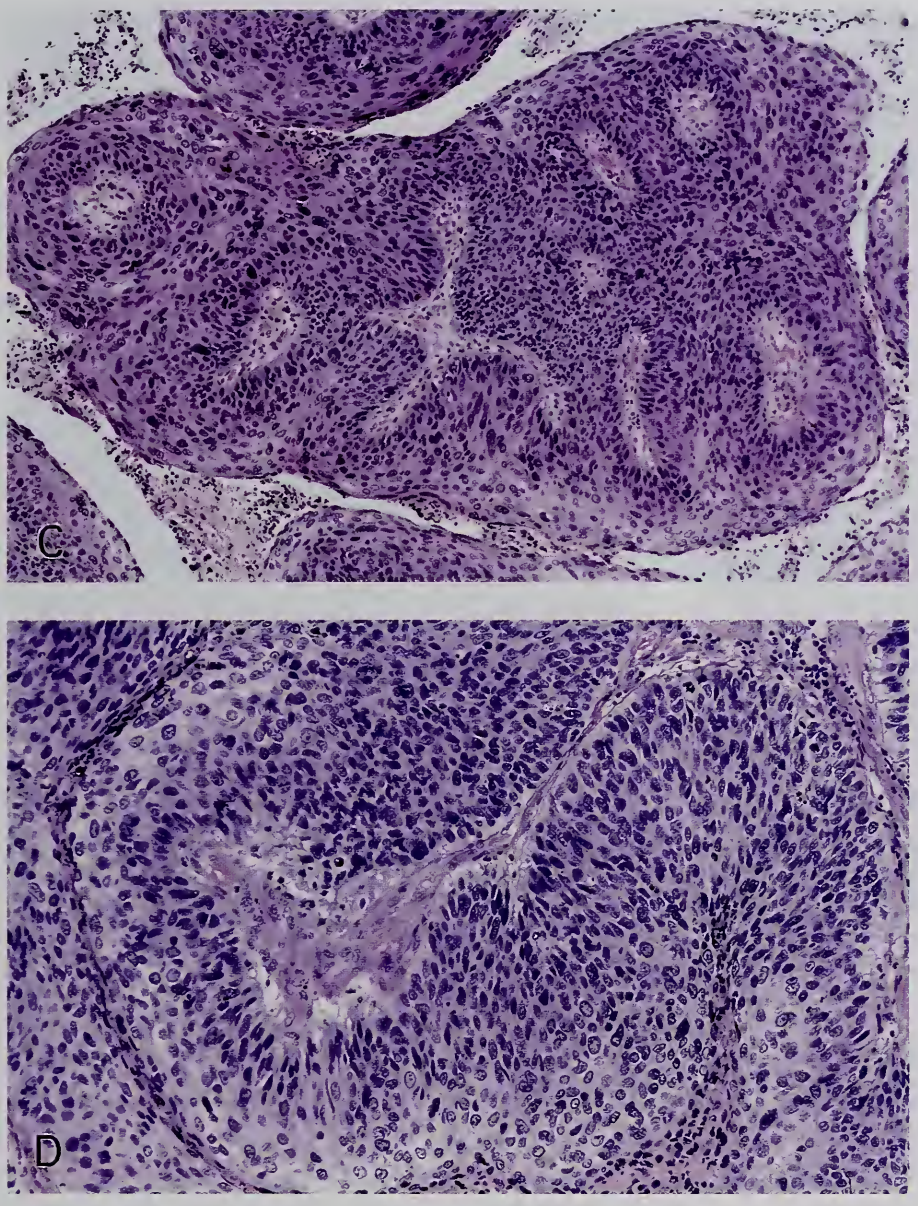


Figure 5-54 (Continued)

C: A papilla is covered by acanthotic atypical immature squamous epithelium with fibrovascular cores.

D: The epithelium is identical to that of a flat HSIL.

Histologically similar neoplasms occur in the nasopharynx, salivary gland, breast, and thymus, and the terms *lymphoepithelioma* and *medullary carcinoma* have been applied to them (151,154,155,276). We prefer the designation lymphoepithelioma-like carcinoma.

These are uncommon tumors and probably represent less than 1 percent of all primary cervical neoplasms, although they appear to be more common in Asia where some series have reported that they account for nearly 6 percent of all cervical carcinomas (162). In a recent study of 15 cases, Epstein-Barr virus (EBV) was detected by PCR in 11 (73 percent) of 15 lymphoepithelioma-like carcinomas compared to 4 of 15 (27 percent) of the usual type of cervical squamous cell carcinoma. PCR studies may be misleading, however, as the EBV signal may be coming from the lymphoid stroma rather than the tumor. Interestingly, the rate of detection of HPV 16 and 18 was significantly lower in the lymphoepithelioma-like carcinomas (20 percent) compared to the typical squamous carcinomas of the cervix (80 percent) (407).

Microscopically, lymphoepithelioma-like carcinomas are characterized by a circumscribed margin and nests of undifferentiated cells with abundant cytoplasm and uniform vesicular nuclei. The cell borders tend to be indistinct and form what has been described as a syncytium (276). The nests of neoplastic epithelial cells are surrounded by an intense inflammatory

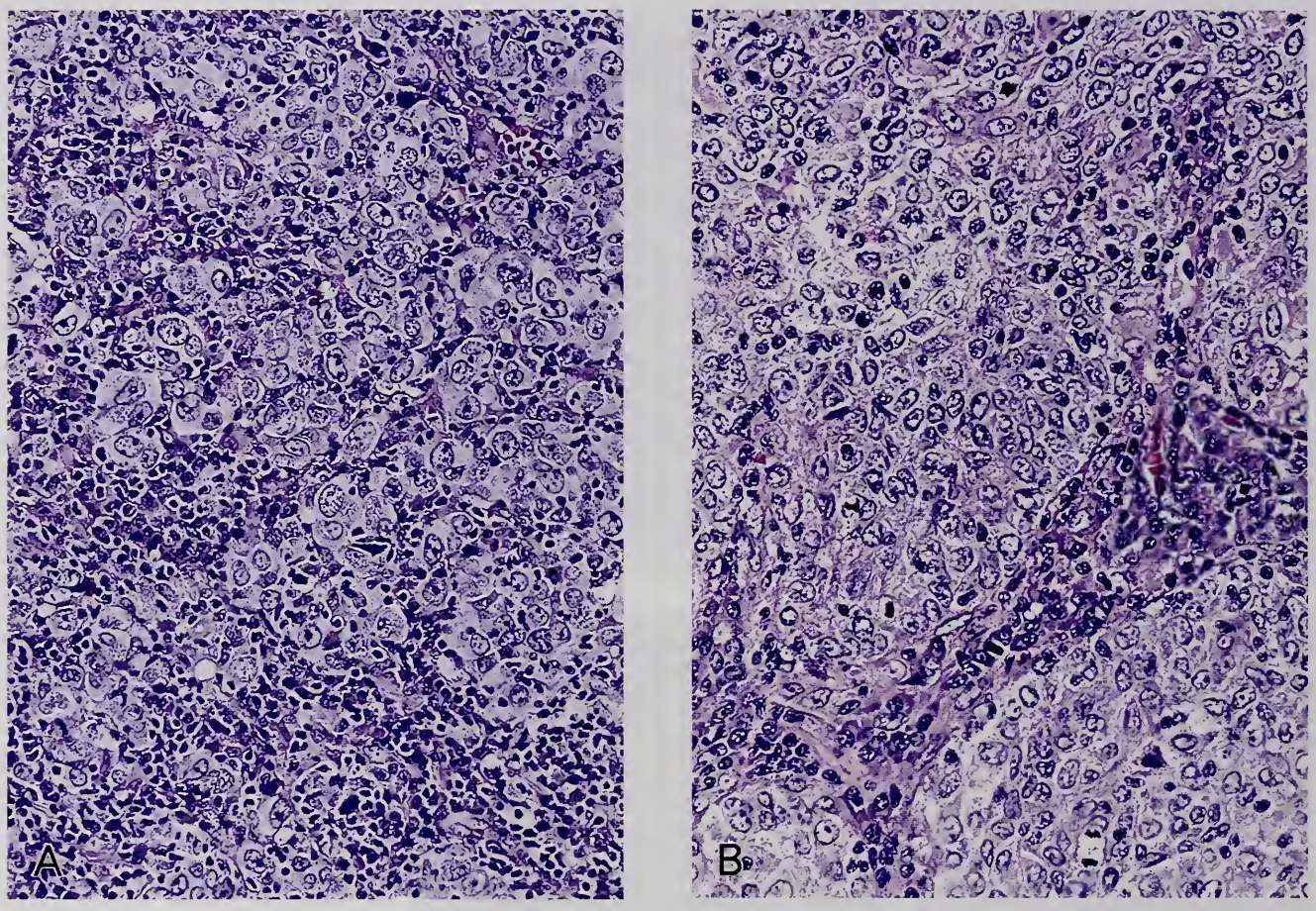


Figure 5-55

LYMPHOEPITHELIOMA-LIKE CARCINOMA

A: Individual carcinoma cells with large vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm are intimately admixed with a non-neoplastic lymphoid infiltrate.

B: Syncytial aggregates of tumor cells have moderate amounts of eosinophilic cytoplasm, indistinct cell borders, and enlarged nuclei with vesicular chromatin and evident nucleoli.

reaction consisting of lymphocytes, plasma cells, and eosinophils (fig. 5-55).

Lymphoepithelioma-like carcinoma should be distinguished from glassy cell carcinoma, which has a poorer prognosis. Glassy cell carcinoma is characterized by nests of undifferentiated cells associated with a marked inflammatory response. Unlike the cells of lymphoepithelioma-like carcinoma, the cells of glassy cell carcinoma have distinct cell borders, ground-glass cytoplasm, nuclei with prominent nucleoli, and much higher mitotic activity. Lymphoepithelioma-like carcinoma is distinguished from the more commonly encountered nonkeratinizing squamous cell carcinoma, associated with marked inflammation, by less marked nuclear pleomorphism and hyperchromasia and by a lack of distinct cell borders. Confusion with a lymphoproliferative disorder can be avoided by immunohistochemical testing for cytokeratin, epithelial membrane antigen (EMA), and leukocyte common antigen (LCA).

In one of the largest studies from Japan, lymphoepithelioma-like carcinoma was associated with a lower frequency of regional lymph node metastasis and a significantly better prognosis when stratified according to stage (162). Some studies have analyzed the behavior of cervical tumors treated by surgical procedures and radiotherapy according to the extent of lymphoplasmacytic response (201) and stromal eosinophilia (47,202). Although the findings have been inconclusive due to the small number of cases, patients with tumors showing a marked

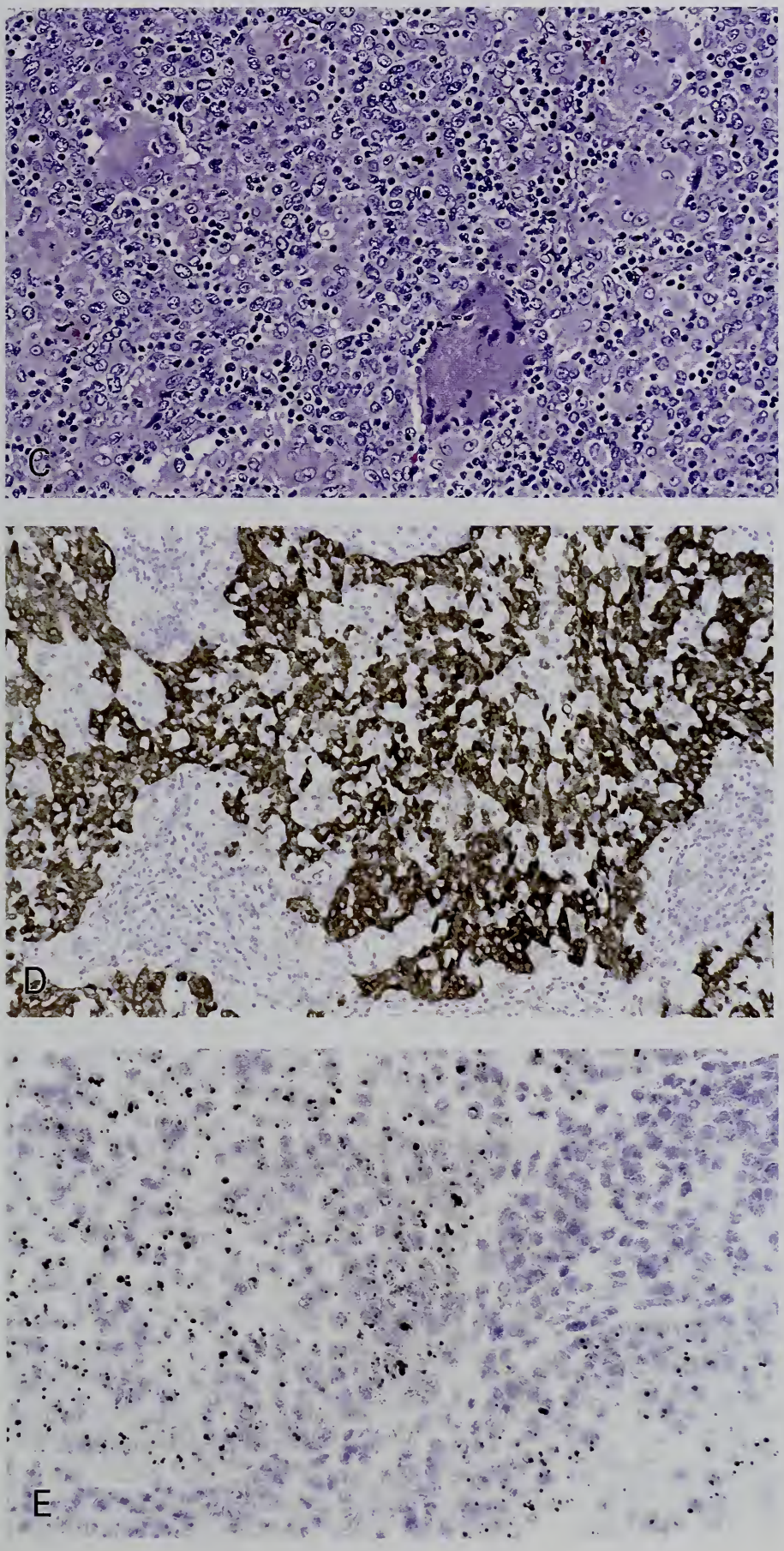


Figure 5-55 (Continued)

C: The tumor is admixed with lymphocytes and multinucleated giant cells.

D: Immunohistochemical stain for p16 highlights the neoplastic epithelial cells.

E: In situ hybridization for HPV 16 demonstrates the characteristic punctate nuclear signal indicating the presence of high-risk HPV.

lymphoplasmacytic response appear to have a higher survival rate than those in whom the response is minimal. A similar improvement in survival associated with marked eosinophilic infiltration has been suggested, but the results were not significant (202). These studies did not focus on lymphoepithelioma-like carcinoma specifically, although some tumors were probably included among the reported cases.

GLANDULAR LESIONS

Endocervical Polyp

Endocervical polyps are usually small but sometimes attain a large size (243); typically, they are solitary, but may be multiple. Polyps often do not produce symptoms, but they may be associated with postcoital bleeding or discharge.

Microscopically, endocervical polyps are covered by varying amounts of squamous and columnar epithelium, depending on their location. Those that are high in the endocervical canal are covered by glandular epithelium, whereas those that arise in the transformation zone may also be covered by squamous epithelium. The stroma is composed of fibrous or fibromuscular tissue; thick-walled blood vessels are present within the stromal core and extend to the base of the polyp. The stromal cells are typically bland but are occasionally plump with prominent nucleoli, especially if inflammation is present. There is no increase in mitotic activity. On occasion, if SIL is present elsewhere in the cervix, it may also be found on the surface of a polyp and sometimes may involve underlying glands.

Müllerian Papilloma

Müllerian papilloma is a rare benign lesion of the cervix (180). It is identical to its counterpart in the vagina (see chapter 6).

Tunnel Clusters

Tunnel clusters are common, typically incidental, lesions, that may be recognizable on gross examination. Tunnel clusters are divided into type A (noncystic) and type B (cystic) forms (110). The type B lesions have been reported in 6 percent of hysterectomy specimens and 10 percent of cone biopsies (359).

This benign alteration of endocervical glands is composed of a nodular aggregate or aggregates of dilated glands of the same size near the epithelial surface. The outline of the glandular aggregate is rounded and nodular, without infiltration at the periphery. The glands are uniformly round and dilated, and contain concentrated mucous fluid. They are lined by a single layer of flat to cuboidal mucinous cells with no mitotic activity, nuclear atypia, or stratification (fig. 5-56). Tunnel clusters with cytologic atypia have been reported (187).

The differential diagnosis includes minimal deviation carcinoma, but the lobulated/nodular configuration, superficial location, and lack of both invasion and cytologic atypia distinguish tunnel clusters from adenocarcinoma (73). Tunnel clusters may result from involution of a cluster of formerly hyperplastic endocervical glands.

Endocervical Glandular Hyperplasia

Endocervical glandular hyperplasia is a proliferation of benign endocervical glands. Some have subdivided the hyperplasia into two types: *lobular endocervical glandular hyperplasia* (271, 296) and *diffuse laminar endocervical glandular hyperplasia* (188). The distinction has little clinical relevance, but recognition that a diffuse form exists is important to avoid overdiagnosis of this benign proliferation as well-differentiated adenocarcinoma. In the lobular form, the proliferation is characterized by crowded, small to medium-sized rounded glands, often centered around a large central gland, thus creating a lobulated pattern (fig. 5-57). The diffuse pattern lacks the lobular configuration (fig. 5-58). Both forms may be confused with minimal deviation adenocarcinoma. Endocervical glandular hyperplasia, in contrast to minimal deviation adenocarcinoma, is well demarcated and superficial. Lack of both cytologic atypia and stromal desmoplasia further facilitates the distinction from minimal deviation adenocarcinoma. It has been suggested that lobular endocervical glandular hyperplasia may be a precursor of minimal deviation adenocarcinoma.

Microglandular Hyperplasia

Definition. *Microglandular hyperplasia* is a complex crowded proliferation of endocervical glandular epithelium that was initially recognized in patients taking oral contraceptives (400,428).

General Features. Microglandular hyperplasia may occur in pregnant women, but the

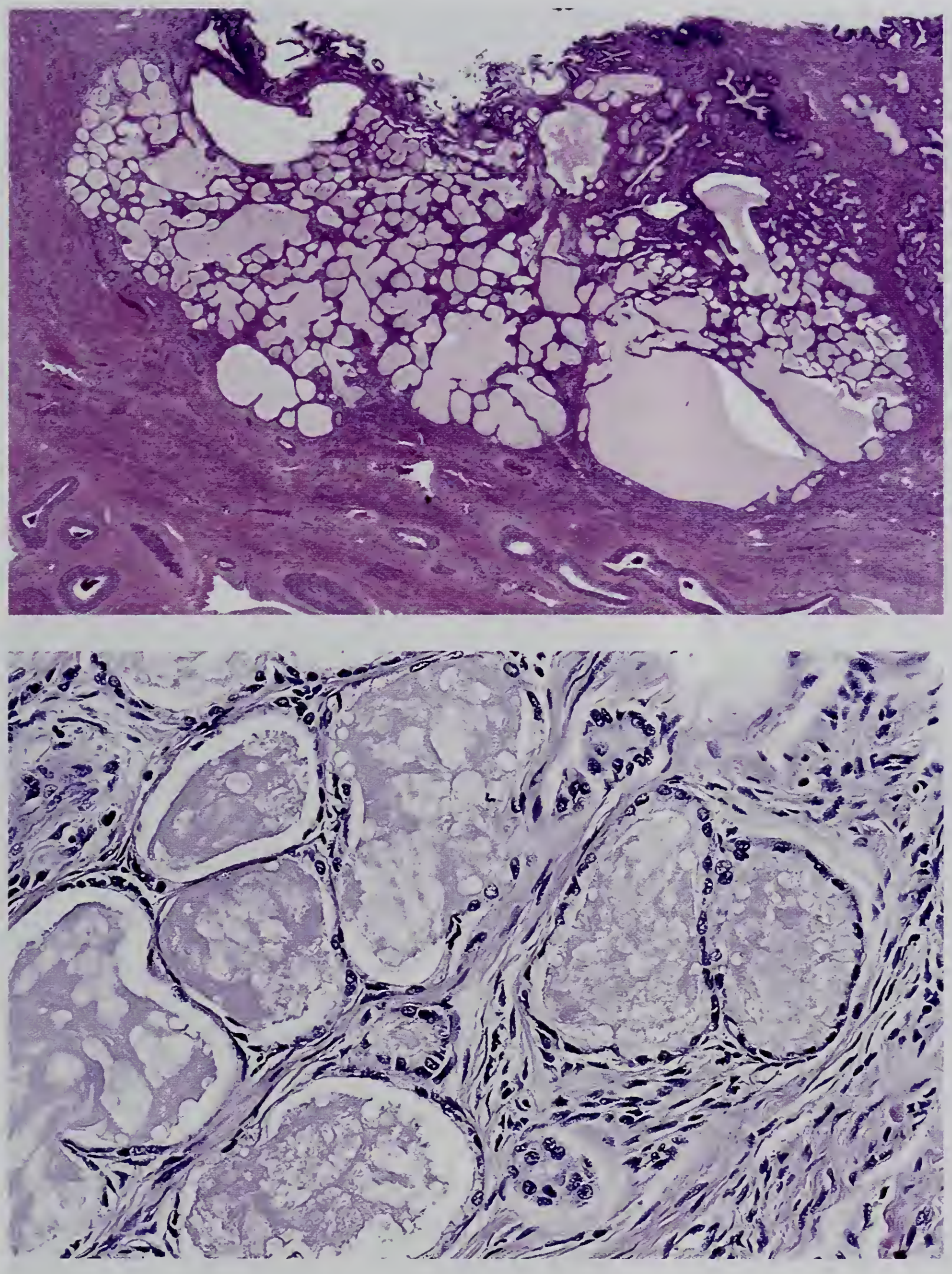


Figure 5-56

ENDOCERVICAL TUNNEL CLUSTERS

Top: A circumscribed, lobulated aggregate of clustered, dilated endocervical glands is situated in the superficial cervical stroma.

Bottom: Dilated endocervical glands are lined by attenuated mucinous epithelium and filled with mucinous eosinophilic secretions.

lesion is usually smaller than that related to oral contraceptive use. Postmenopausal women taking estrogen-progestin replacement therapy may also have microglandular hyperplasia; however, women taking oral contraceptives are likely to have more extensive microglandular hyperplasia, squamous metaplasia, inflammation, and edema than those without a history of oral contraceptive use. The effects of oral contraceptives on the endocervical glands include increased numbers of glands and hypersecretion, with microglandular hyperplasia in about 3 percent of the cases (123). Since the lesion is found in postmenopausal women, women who are only on estrogen, and women who are not on any hormones, a causal association with oral contraceptives and pregnancy is questioned (145).

Gross Findings. Microglandular hyperplasia is often polypoid and may be unifocal or multifocal. Early lesions may appear sessile.

Microscopic Findings. Densely crowded small glands are lined by a single layer of cuboidal cells containing varying amounts of mucin. The cytoplasm is clear to finely granular and amphophilic to eosinophilic, and typically shows subnuclear vacuolization. Nuclei are uniformly small and round and have fine, evenly dispersed chromatin (fig. 5-59). Nuclear enlargement

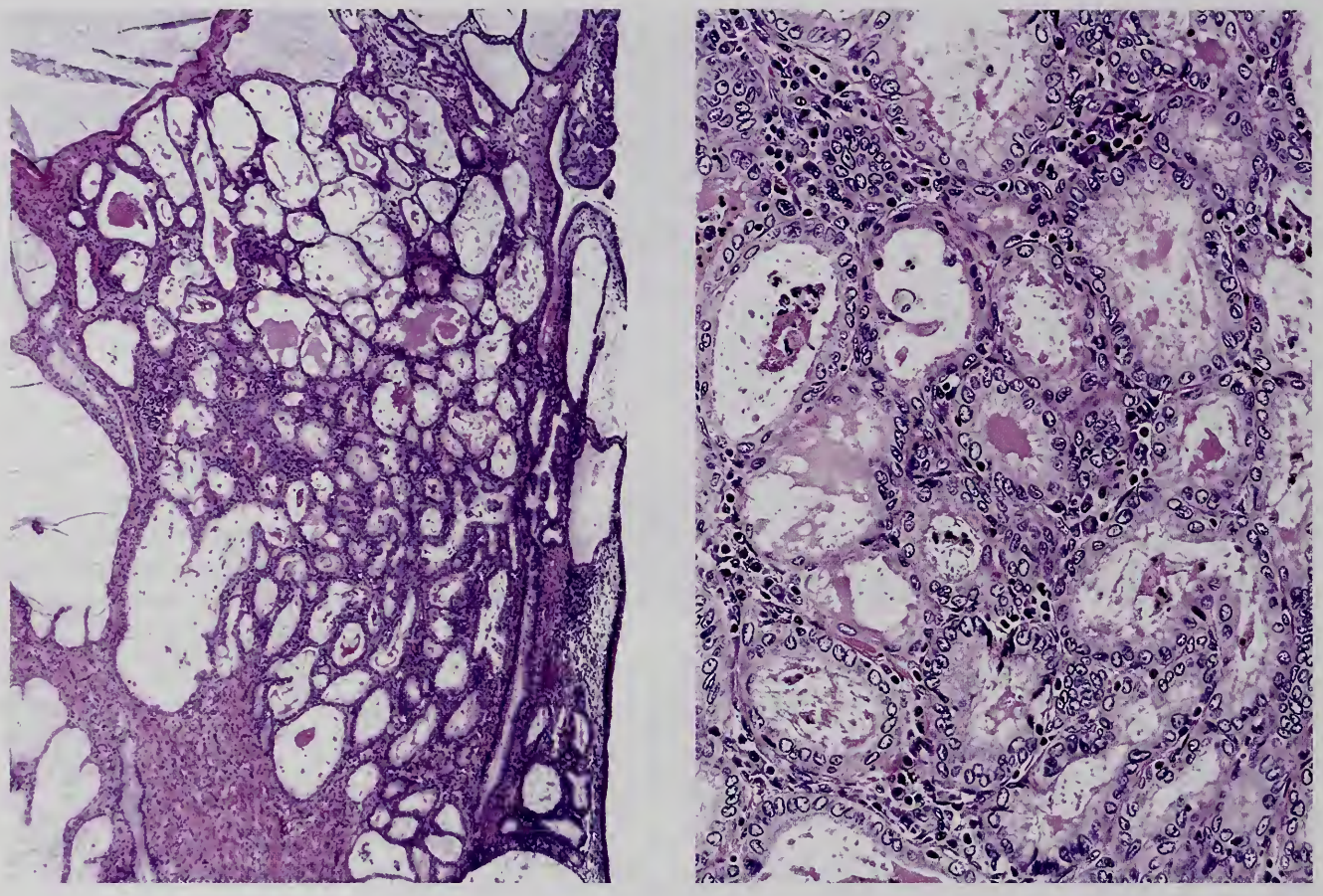


Figure 5-57

ENDOCERVICAL GLANDULAR HYPERPLASIA

Left: The lobular form of hyperplasia is characterized by cystic and noncystic endocervical glands arranged in circumscribed aggregates.

Right: At higher magnification, noncystic, tightly clustered endocervical glands exhibit rounded vesicular nuclei with evident nucleoli, reminiscent of the atypia seen in minimal deviation adenocarcinoma.

and hyperchromasia are generally minimal or absent, unless an Arias-Stella reaction has supervened. Mitotic figures are absent or sparse. The glandular cells stain weakly with mucicarmine, Alcian blue, and periodic acid–Schiff (PAS) with diastase digestion, but the secretion within the lumen of the gland is strongly positive. Neutrophils are typically present within gland lumens. Foci of squamous metaplasia may be present. The stroma often contains lymphocytes, plasma cells, and eosinophils. Stromal edema is common and usually a few stromal cells are present, compressed between the glands.

Unusual forms of microglandular hyperplasia exist. These may be mucinous or solid or have areas of hyalinization (192,439). In the mucinous variant, islands and nests of detached cells float in pools of mucin. The solid pattern is characterized by sheets of clear cells with slightly vacuolated cytoplasm. The cells have small, centrally positioned, bland or slightly atypical nuclei. In both the mucinous and solid patterns, atypia is minimal and mitotic figures are largely absent. Abundant stromal hyalinization also occurs in some lesions. These unusual patterns are associated with areas of more typical microglandular hyperplasia, thereby permitting the correct diagnosis. Cervical cytologic specimens may demonstrate cellular sheets of reactive or atypical endocervical cells with nuclear enlargement, sometimes leading to an interpretation of atypical glandular cells of undetermined significance. On occasion, smears contain small metaplastic-appearing cells with shrunken, pyknotic nuclei arranged in a linear fashion in the endocervical mucus.

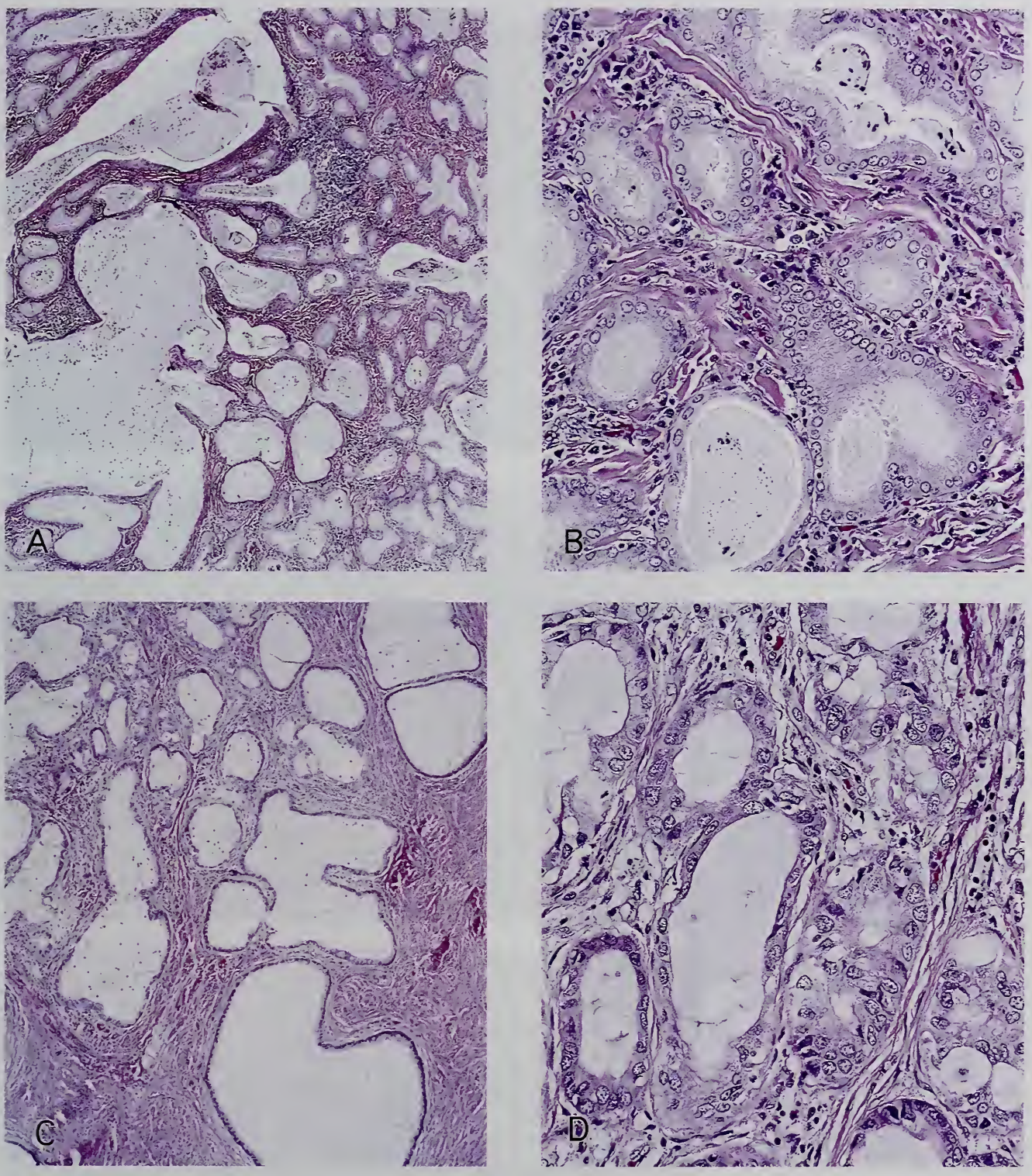


Figure 5-58

ENDOCERVICAL GLANDULAR HYPERPLASIA

A: The diffuse pattern of hyperplasia simulates well-differentiated (minimal deviation) adenocarcinoma.

B: At higher magnification, noncystic glands exhibiting rounded nuclei with vesicular chromatin and evident nucleoli situated deeper in the cervical stroma within diffuse hyperplasia simulate well-differentiated (minimal deviation) adenocarcinoma.

C: Cystic glands appear noninfiltrative but lack an obvious lobulated pattern.

D: At higher magnification, noncystic glands exhibit focal cribriform growth and nuclear atypia, simulating well-differentiated (minimal deviation) adenocarcinoma.

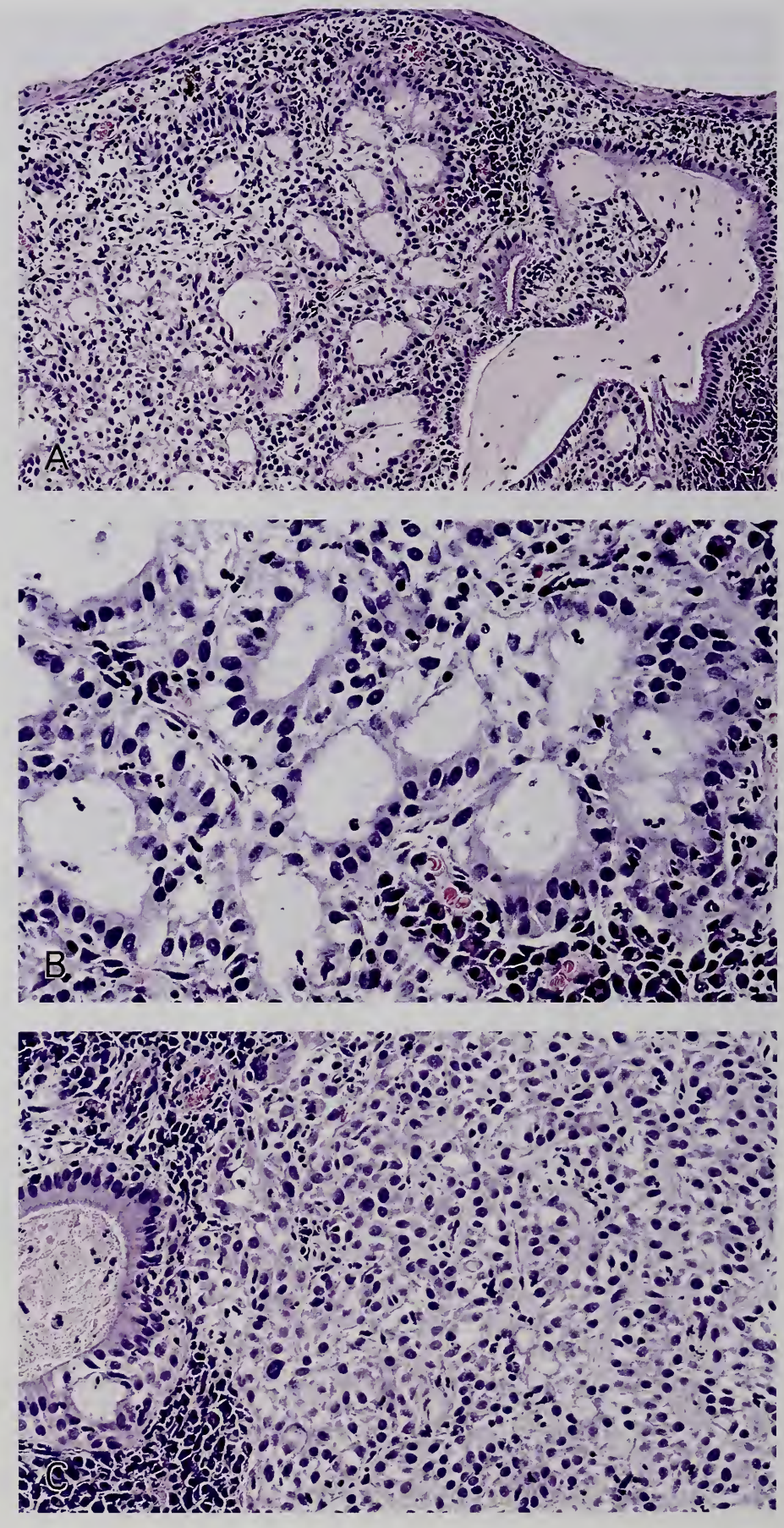


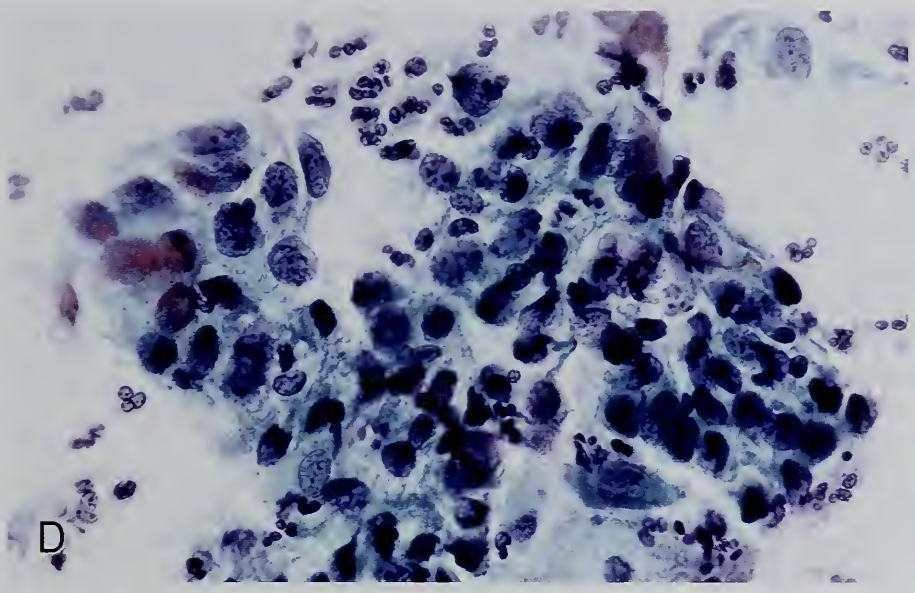
Figure 5-59

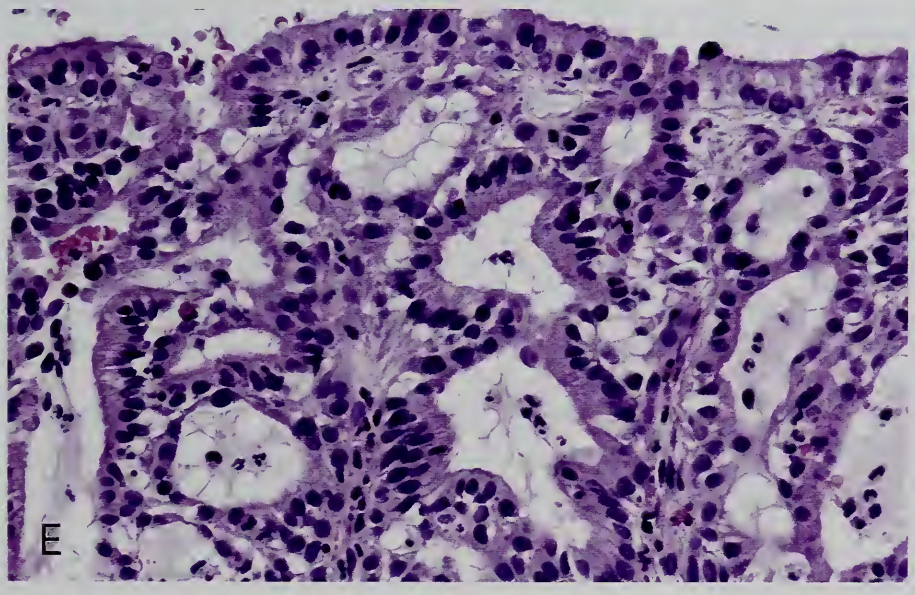
MICROGLANDULAR HYPERPLASIA

A: Crowded and fused, small and focally dilated endocervical glands are situated within chronically inflamed stroma.

B: Fused small endocervical glands have subnuclear vacuoles. A prominent inflammatory cell infiltrate with numerous plasma cells is present.

C: A solid pattern of glands with numerous subnuclear vacuoles simulates clear cell carcinoma.





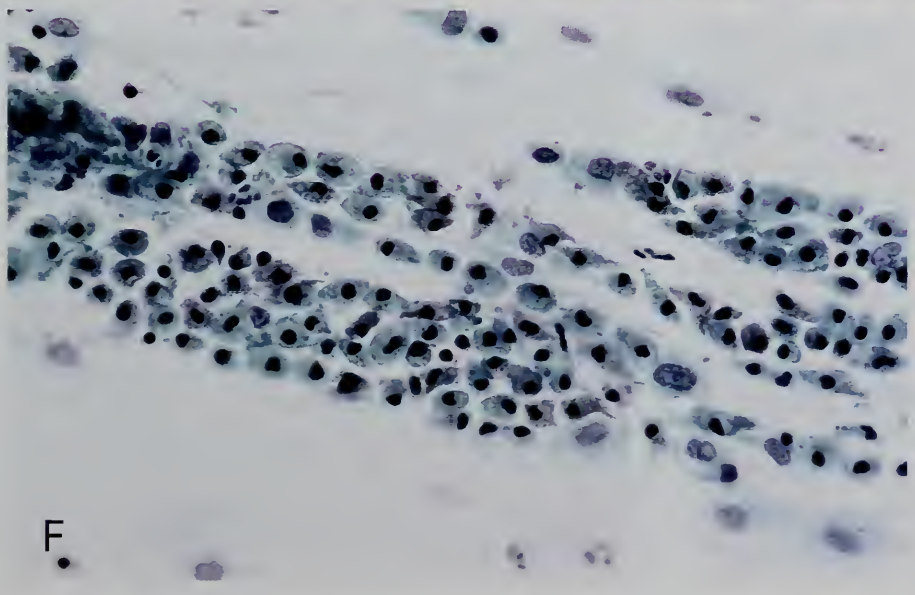


Figure 5-59 (Continued)

D: Aggregates of endocervical cells with enlarged, hyperchromatic nuclei can be interpreted as atypical glandular cells in cytologic preparations.

E: Fused endocervical glands contain occasional enlarged, hyperchromatic nuclei, which can explain the finding of atypical glandular cells in cytologic preparations (biopsy specimen corresponding to the cytologic specimen illustrated in figure D).

F: Streams of small cells with vacuolated cytoplasm and pyknotic nuclei can be seen in cytologic smears from patients with follow-up biopsies demonstrating microglandular hyperplasia.

Differential Diagnosis. Microglandular hyperplasia must be distinguished from clear cell carcinoma. The latter tends to form papillary processes and is composed of more open glands and tubules. In addition, clear cell carcinoma often contains hobnail cells with enlarged, hyperchromatic nuclei protruding into the lumens of glands and tubules. Clear cell carcinoma also has easily recognized mitotic figures and cells showing marked nuclear atypia. The absence of mitotic figures in the densely packed glands of microglandular hyperplasia is a particularly helpful discriminating feature. The presence of a high glycogen content and absence of squamous metaplasia also help distinguish clear cell carcinoma from microglandular hyperplasia.

Adenocarcinoma may also arise in a cervix with microglandular hyperplasia, but the nuclear atypia, high mitotic activity, invasion into the cervical stroma, and histologic patterns typical of adenocarcinoma of the cervix should help differentiate the two. A negative immunostain for CEA usually supports a diagnosis of microglandular hyperplasia; however, cervical adenocarcinomas are occasionally negative or only focally positive for CEA.

Mesonephric Remnants

Mesonephric remnants occur in up to 22 percent of cervices. Their frequency varies with the type of specimen because they are seldom encountered in biopsy specimens, but are relatively common in conization and hysterectomy specimens in which deep and lateral portions of the cervix are routinely examined. Mesonephric remnants are asymptomatic and are incidental findings because they are too small to be seen visibly.

Mesonephric remnants occur most commonly midway through the cervix, in the lamina propria of the lateral wall beneath the junction of the exocervix with the endocervix. They are typically composed of small tubular glands clustered in lobules that often surround a main branching duct. The main duct, when present, has an ampullary character. The tubules are distinctive and composed of a single layer of flat to cuboidal cells. A prominent basement membrane surrounds the tubules, and dense eosinophilic or hyaline secretion is usually present within the lumens. The cytoplasm does not stain with PAS or mucicarmine and the luminal secretions are also negative for mucicarmine. Mesonephric tubules differ from endocervical glands by their small size, deep location, clustering about a main duct, absence of mucin production, presence of a basement membrane about tubules, and dense intraluminal eosinophilic secretion.

Cysts may develop from mesonephric remnants. These are solitary and lined by flattened or cuboidal epithelium. Squamous metaplasia rarely occurs in the cystic ampullary portion of mesonephric duct remnants.

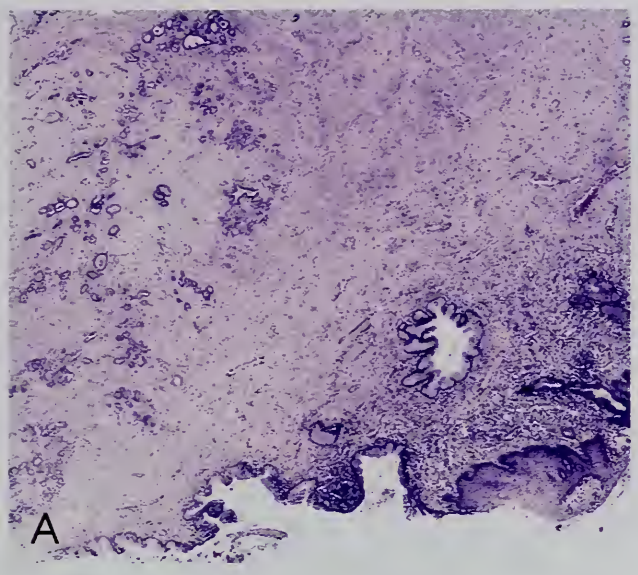
Mesonephric Hyperplasia

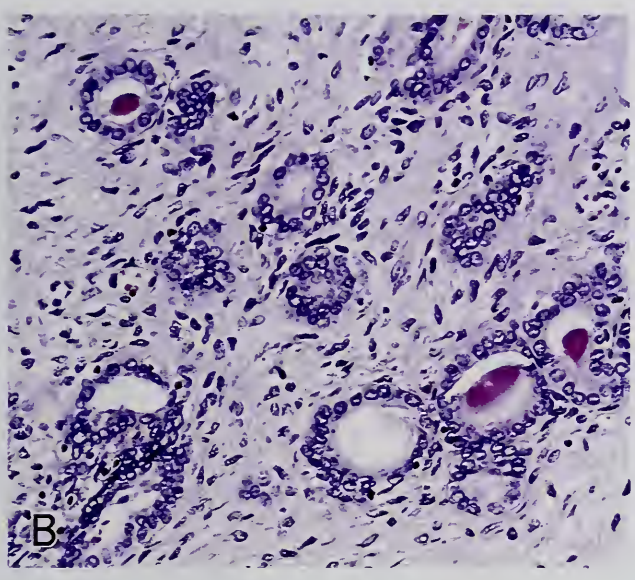
Mesonephric remnants ordinarily occupy only a few millimeters of the deep cervical stroma. A diagnosis of *mesonephric hyperplasia* is based on the presence of a prominent increase in the number of tubules, an increase in lobule size, and diffuse or extensive involvement of the cervix. The tubules may involve almost the full thickness of the cervix and may be quite superficial. The presence of a main branching duct with surrounding smaller tubules imparting a lobular appearance, as seen with remnants, is often seen in hyperplasia as well. The tubules are generally similar to those comprising remnants, being lined by cuboidal cells and containing dense eosinophilic secretions (fig. 5-60). In mesonephric hyperplasia, the cells show some variation in size and shape, as well as nuclear enlargement and occasional mitotic activity (up to 2 per 10 high-power fields) (23,166). Rare cases of mesonephric adenocarcinoma have been described (see below).

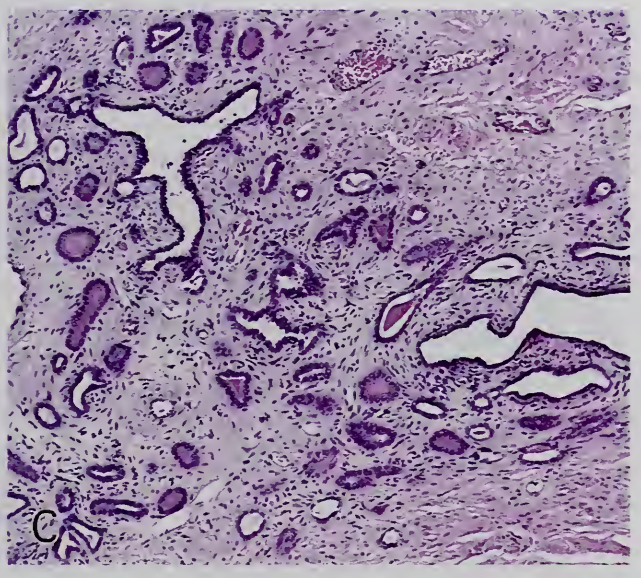
Arias-Stella Reaction

The *Arias-Stella reaction* typically occurs in the endometrium in association with pregnancy, including ectopic gestation and gestational trophoblastic disease. Occasionally, it occurs in endocervical glands under these circumstances and is similar in appearance to the endometrial lesion.

Microscopically, the Arias-Stella reaction is characterized by glands lined by vacuolated epithelial cells that have a hypersecretory appearance. The nuclei are pleomorphic, enlarged, and hyperchromatic, and typically protrude into the glandular lumen with little accompanying cytoplasm, resulting in a hobnail appearance (fig. 5-61). The Arias-Stella reaction







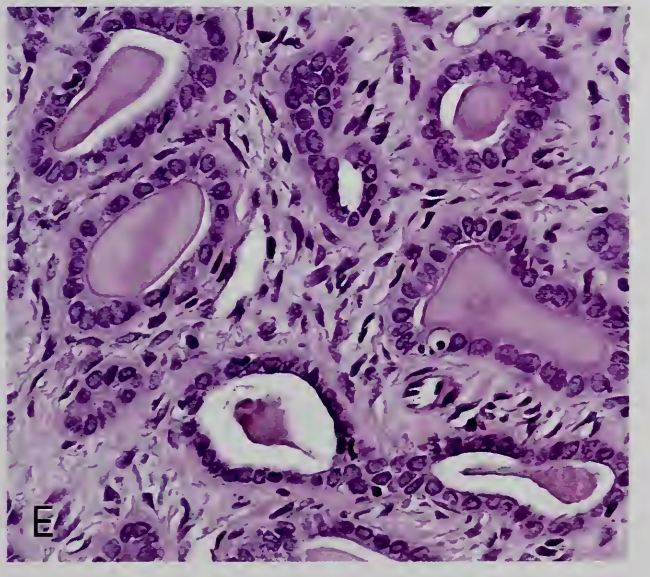


Figure 5-60

MESONEPHRIC HYPERPLASIA

A: A proliferation of clustered small glands is situated in the deep cervical stroma, beneath the transformation zone, lying just beneath endocervical glands.

B: Small tubular glands contain dense eosinophilic secretions and are lined by cuboidal epithelium composed of cells with uniform round nuclei and minimal cytoplasm.

C: Branching ductal structures are surrounded by smaller acini.

D: Small tubular glands contain dense eosinophilic secretions and surround a branching ductal structure.

E: Tubular glands contain dense eosinophilic secretions and are lined by a single layer of cells with uniform round nuclei.

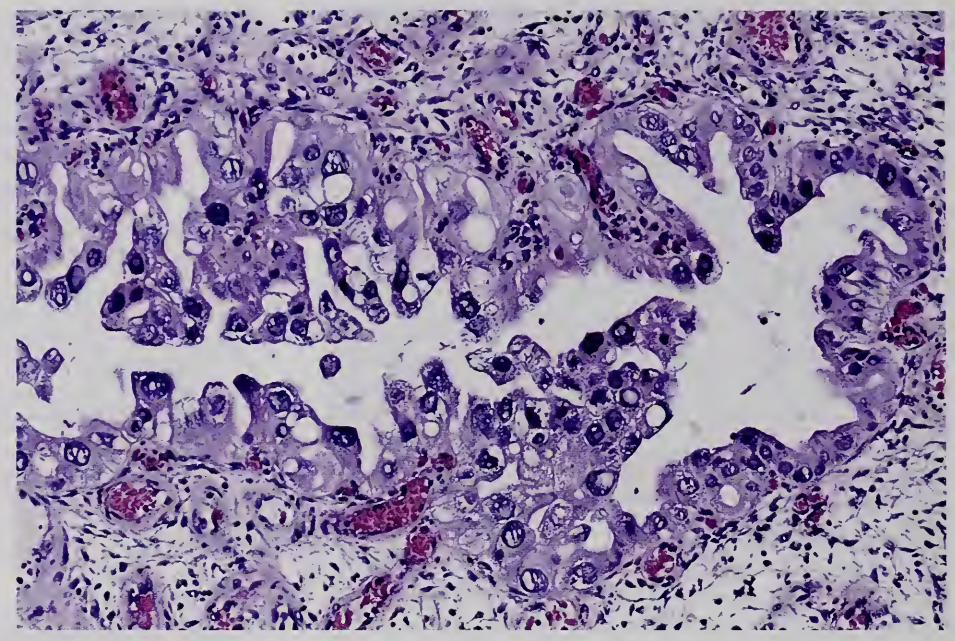


Figure 5-61

ARIAS-STELLA REACTION

An endocervical gland is lined by tufted epithelium containing cells with eosinophilic to clear cytoplasm and occasional enlarged, atypical and hyperchromatic nuclei with hobnail features, simulating clear cell carcinoma.

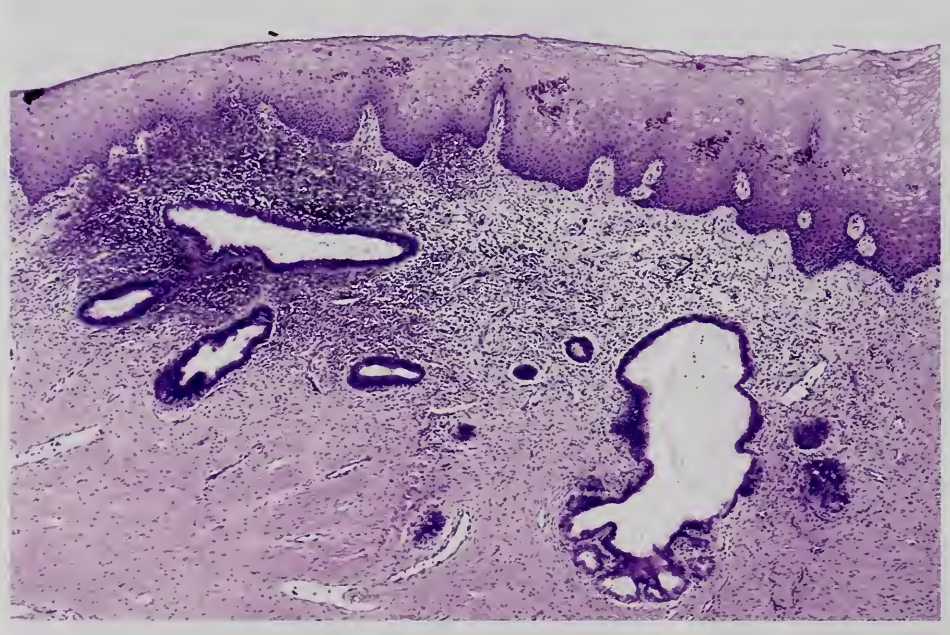


Figure 5-62

ENDOMETRIOSIS

Endometrial type glands surrounded by endometrial type stroma are present beneath cervical squamous mucosa.

should not be confused with clear cell carcinoma. In contrast to clear cell carcinoma, the Arias-Stella reaction is associated with other morphologic alterations associated with pregnancy, such as hypersecretory glands and decidual change in stromal cells. In addition, mitotic activity is rarely present in the Arias-Stella reaction compared with clear cell carcinoma (298).

Endometriosis

Usually located on the portio, the combination of endometrial glands and stroma, along with hemofuscin-laden or hemosiderin-laden macrophages, is diagnostic of *endometriosis* (fig. 5-62). If stroma is not present, the lesion cannot be identified with certainty. Immunostains for CD10 assist in identifying endometrial stromal cells but expression of this marker is seen in cervical stromal cells as well so it is not specific for endometrial stroma (261). When stroma is difficult to identify, the distinction from endometrial or tubal metaplasia is based on the cell type and the position of the glands deep to the usual location of the endocervical glands. In instances where only stroma is present (*stromal endometriosis*), the possibility of confusion with an endometrial

stromal sarcoma exists. Stromal endometriosis is distinguished from endometrial and endocervical stromal sarcoma by its small size and failure to infiltrate widely at the periphery (75).

Tubal, Tuboendometrioid, and Endometrioid Metaplasias

Tubal metaplasia is characterized by architecturally normal glands lined by cells that resemble those of the fallopian tube mucosa. Ciliated or clear cells, nonciliated cells, and intercalary (peg) cells are often present (fig. 5-63). Tubal metaplasia usually involves a single gland or a few glands near the squamocolumnar junction and is not associated with inflammation. Rarely, endocervical glands have a pure endometrioid appearance, so-called *endometrioid metaplasia*. More often, there is overlap of tubal and endometrioid cell types, which is referred to as *tuboendometrioid metaplasia* (303). These metaplasias are usually found incidentally, although sometimes the initial manifestation is an abnormal cytologic specimen interpreted as atypical glandular cells. One study has suggested that tuboendometrioid metaplasia may be a sequela to injury resulting from cone biopsy in view of the frequent finding of this lesion at the site of prior cone biopsies in subsequent hysterectomy specimens (178).

Tubal metaplasia is usually CEA negative, but in one study, the metaplastic glands were CEA positive in 39 percent of cases (254). Rarely, tubal metaplasia displays nuclear enlargement, crowding, pseudostratification, and occasional mitotic figures (fig. 5-64). These changes have been found adjacent to adenocarcinoma in situ and occasionally invasive adenocarcinoma. Such lesions have been termed *atypical tubal metaplasia* (356). The association has led some investigators to suggest that this is a premalignant lesion, but in a recent large series, tubal metaplasia, microglandular hyperplasia, and glandular atypia were only rarely identified adjacent to invasive adenocarcinoma; these findings do not support the view that these are precursor lesions (421).

Recently, an unusual type of tubal metaplasia designated *pseudoinfiltrative tubal metaplasia* was reported (418). Because of the haphazard growth pattern, the lesion can be confused with minimal deviation adenocarcinoma. In contrast to the latter, pseudoinfiltrative tubal metaplasia has bland nuclei and no associated stromal desmoplasia. Also, it expresses hormone receptors that are usually absent in minimal deviation adenocarcinoma. Of interest was the association with in utero diethylstilbestrol (DES) exposure in all three of the reported cases, suggesting that this lesion may be an unusual form of DES-related adenosis.

Endocervicosis

Endocervicosis is characterized by the presence of benign endocervical type glands that involve the peritoneum, including the uterine serosa, cul-de-sac, and urinary bladder. The lesion was described in the uterine cervix in women from 29 to 45 years of age, two of whom had a history of a cesarean section (435); the lesion was evident grossly in all four cases.

Endocervicosis is composed of glands of variable size and shape lined by endocervical type epithelium that ranges from columnar to flat. The glands have an infiltrative type growth pattern but nuclear atypia is not present (fig. 5-65). The lesions tend to occur in the outer wall of the cervix and involve the paracervical connective tissue.

Extensive endocervicosis may simulate minimal deviation adenocarcinoma, but in contrast to the latter, the glands of endocervicosis are separated from overlying endocervical glands by connective tissue. In addition, the epithelium in endocervicosis is bland whereas in minimal deviation adenocarcinoma some atypia, even if only focal, is present. Endocervicosis may also resemble an adenomyoma but adenomyomas are composed of smooth muscle in addition to glands and are more sharply circumscribed.

Cysts

Cysts of the cervix are usually the result of a dilated endocervical gland entrapped in the stroma. Some reach 1.5 cm in diameter. Most are multiple and contiguous with cystically dilated Nabothian cysts or normal-sized overlying endocervical glands. A cyst may extend through the endocervix to within 1 mm of the paracervical connective tissue (73).

Most *endocervical glandular cysts* are lined by a single layer of endocervical type cells, which vary from columnar to flattened but are nonetheless mucinous in character. Mitotic

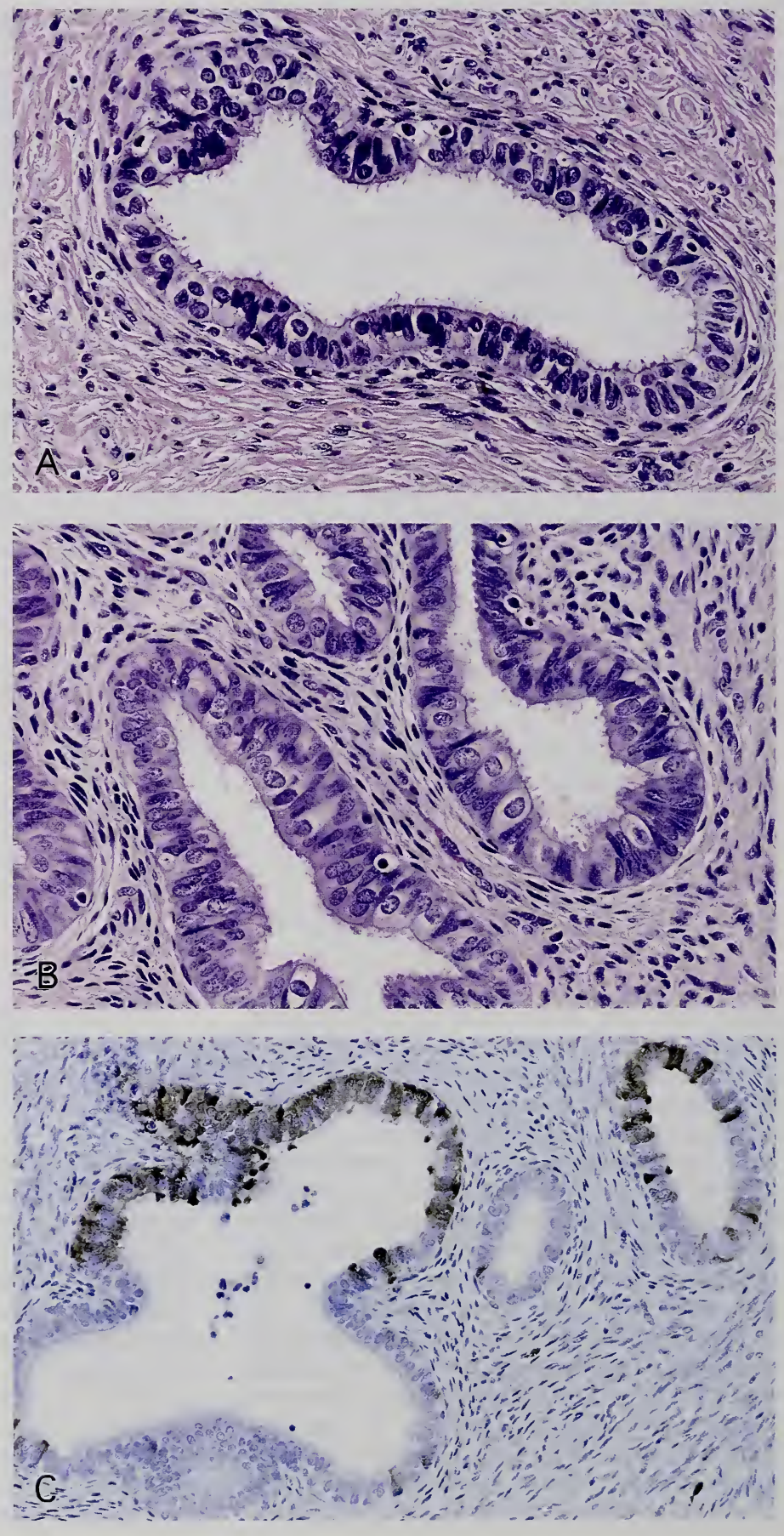


Figure 5-63

TUBAL METAPLASIA

A: Endocervical glandular epithelium is replaced by ciliated epithelium.

B: Epithelium consists of several cell types, including ciliated cells with pale to clear cytoplasm and rounded nuclei, secretory cells, and intercalated cells.

C: Patchy expression of p16 distinguishes tubal metaplasia and other benign endocervical glandular lesions from adenocarcinoma in situ (AIS) which exhibits diffuse expression of p16 (see figs. 5-84 and 5-85).

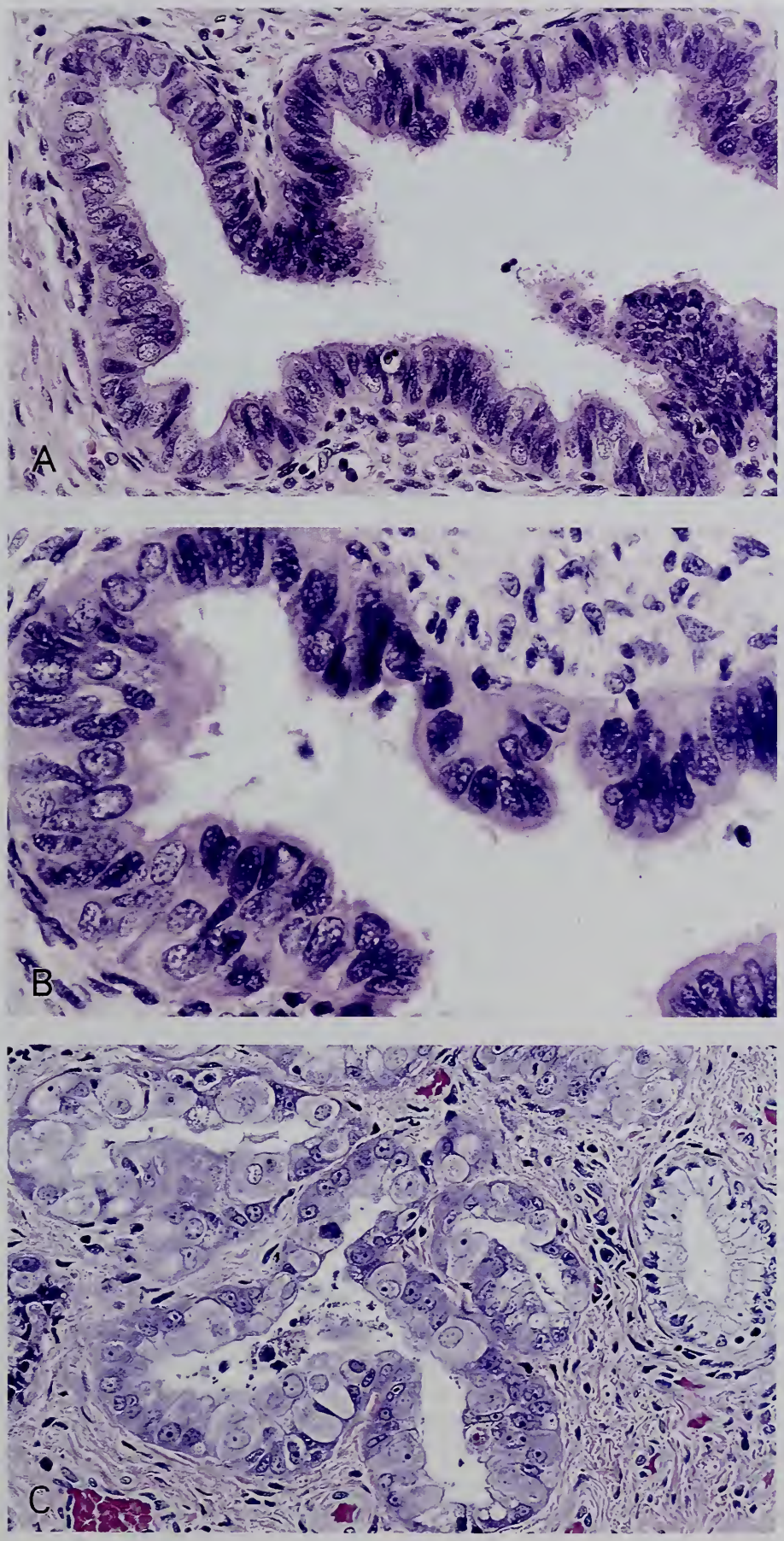


Figure 5-64

ATYPICAL TUBAL METAPLASIA

A: Some cells have enlarged hyperchromatic nuclei and diminished cytoplasm, suggesting the possibility of a glandular intraepithelial lesion.

B: The epithelium exhibits cellular stratification and cells contain enlarged nuclei with granular to smudgy chromatin but cilia are retained on many cells.

C: An unusual example contains large cells with abundant eosinophilic cytoplasm and vesicular nuclei with evident nucleoli, imparting a "pagetoid" appearance.

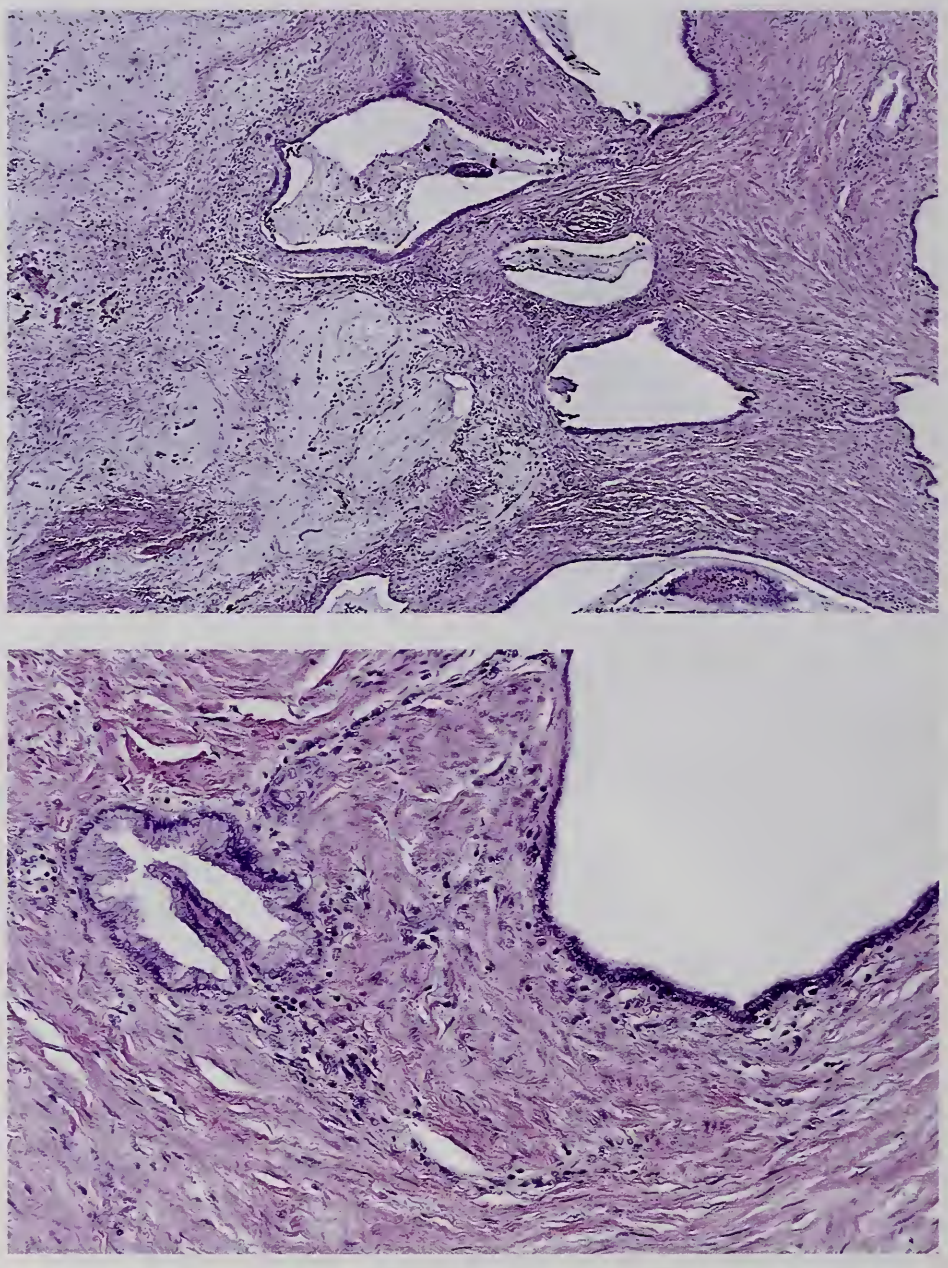


Figure 5-65

ENDOCERVICOSIS

Top: A dilated bland endocervical gland and dissecting mucin extend deep into the cervical wall and paracervical soft tissue.

Bottom: Dilated and nondilated endocervical glands are lined, respectively, by attenuated nonspecific cuboidal and mucinous epithelium lacking nuclear atypia.

figures and cell stratification are not observed. The luminal borders are usually mucin positive. Minimal deviation adenocarcinoma may form large mucinous cysts also, but in these the cells are large, the epithelium is hyperplastic in appearance, and the cysts are a component of a larger proliferation of glands of abnormal size and shape.

Less common types of benign cysts include a cystic gland within endometriosis or one showing tubal metaplasia. These are not grossly cystic and are superficial cystically dilated glands rather than true cysts. Cysts derived from the mesonephric duct are usually lined by flattened epithelium or cuboidal epithelium deep within the stroma, unconnected to endocervical glands, and do not contain mucin. Squamous metaplasia may rarely develop in some of these.

Intestinal Metaplasia

Intestinal metaplasia may occur within adenocarcinoma in situ and invasive adenocarcinoma of the endocervix. Goblet cells are present, and argentaffin and Paneth cells are occasionally seen (406). A lesion resembling villous adenoma and associated with nearby invasive adenocarcinoma has been described (270).

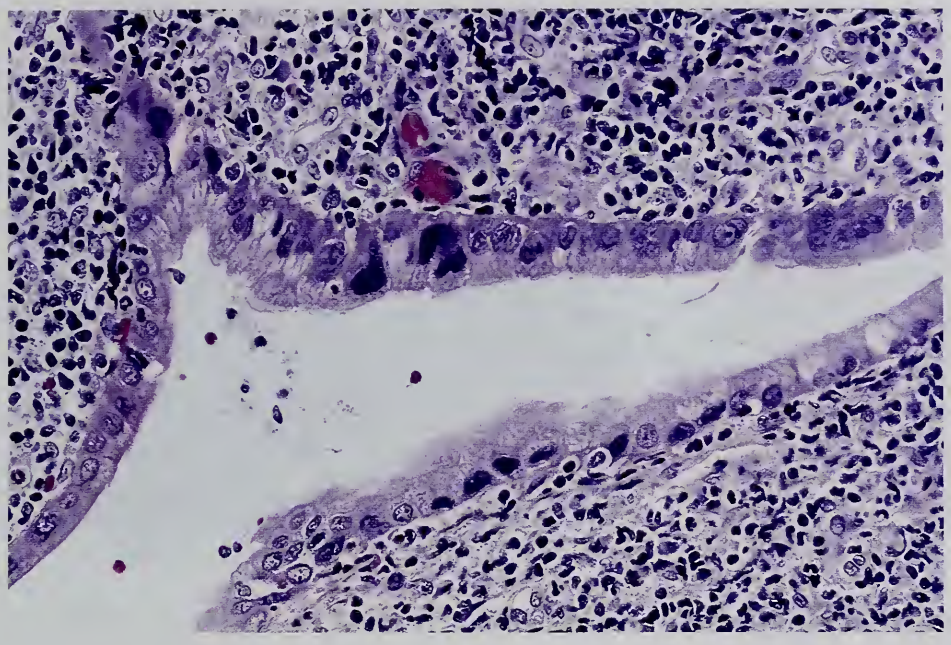


Figure 5-66

GLANDULAR ATYPIA

Endocervical glandular epithelium is surrounded by a dense chronic inflammatory cell infiltrate and contains some enlarged, euchromatic nuclei and occasional cells with smudgy hyperchromatic nuclei. Mitotic figures and apoptotic bodies are lacking.

Atypical Oxyphilic Metaplasia

Atypical oxyphilic metaplasia consists of endocervical cells with abundant eosinophilic cytoplasm and atypical nuclei with smudged, hyperchromatic chromatin. The nuclei may be multilobated and nucleoli are often prominent. Mitoses are generally lacking (186). This benign lesion is identical to eosinophilic metaplasia in the endometrium. It has no known clinical significance.

Ectopic Prostatic Tissue

Clusters of benign prostatic glands with cribriform and papillary patterns and focal squamous metaplasia have been reported in the endocervical stroma. The lesion can be confused with mesonephric rests, microglandular hyperplasia, or adenocarcinoma in situ but the glands are positive for prostate-specific antigen and prostate-specific acid phosphatase (234,297). It has been thought to represent an embryonic rest but most likely is an unusual form of metaplasia.

Glandular Atypia

Atypia involving endocervical glandular epithelium is associated with marked inflammation, often near ulceration of the overlying surface, or radiation exposure. Characteristically, the epithelium lining the glands is not stratified. The nuclei are enlarged, pleomorphic, hyperchromatic, and sometimes multiple, with some having smudged chromatin. Nucleoli may be present. Mitotic figures are rare (figs. 5-66, 5-67, 5-71, 5-74).

Reactive atypia is manifested in cytologic specimens as sheets of endocervical cells exhibiting nuclear crowding, overlapping, enlargement, and prominent nucleoli (figs. 5-68–5-70). In some instances, nuclear pleomorphism and hyperchromasia can lead to an interpretation of atypical glandular cells of undetermined significance. Vacuolated atypical glandular cells suggesting endometrial or endocervical endometrioid carcinoma are associated with intrauterine device usage (fig. 5-72). Cytomegalovirus infection can result in enlarged, atypical-appearing endocervical cell nuclei containing viral inclusions (fig. 5-73). Occasionally, there is no associated lesion that can account for the reactive change.

Reactive atypia is generally distinguished from adenocarcinoma in situ by the lack of epithelial stratification, degenerative or reactive type changes in nuclear chromatin (smudged in the former and vesicular with discrete nucleoli in the latter) rather than granular hyperchromasia, and a paucity of mitotic activity and apoptotic bodies (fig. 5-74). Occasionally, glands exhibit some features of adenocarcinoma in situ but not in sufficient extent or degree to qualify unequivocally as such. The terms *endocervical glandular dysplasia* and *glandular intraepithelial*

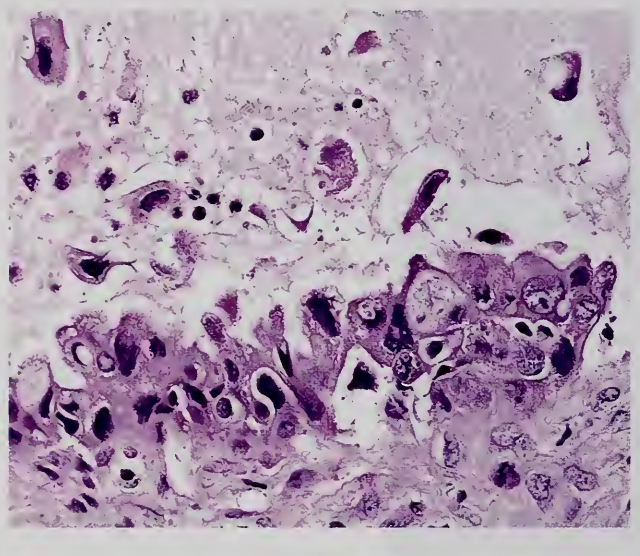


Figure 5-67

RADIATION ATYPIA

Endocervical glandular epithelium contains cells with abundant eosinophilic and vacuolated cytoplasm and occasional enlarged nuclei with vesicular to smudgy chromatin.

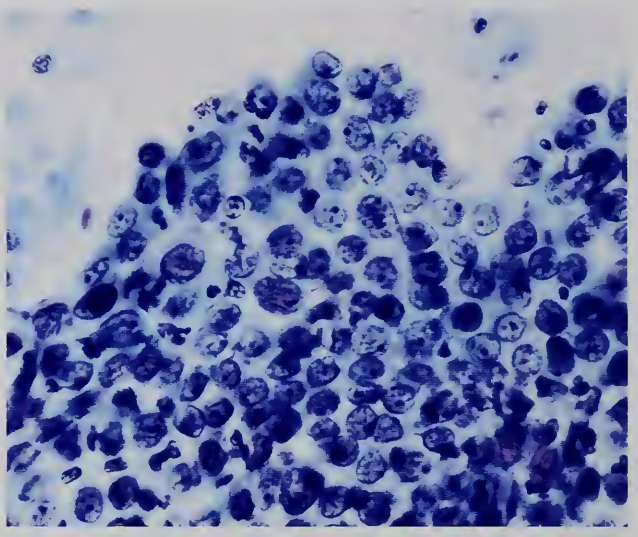
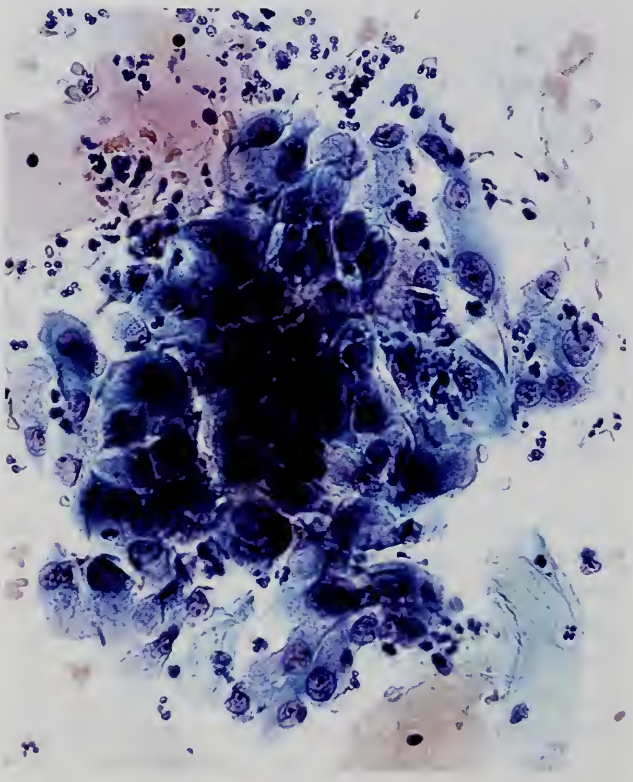


Figure 5-68

REACTIVE ENDOCERVICAL GLANDULAR CELLS

Crowded endocervical cells have enlarged nuclei, uniform vesicular chromatin, and small nucleoli.



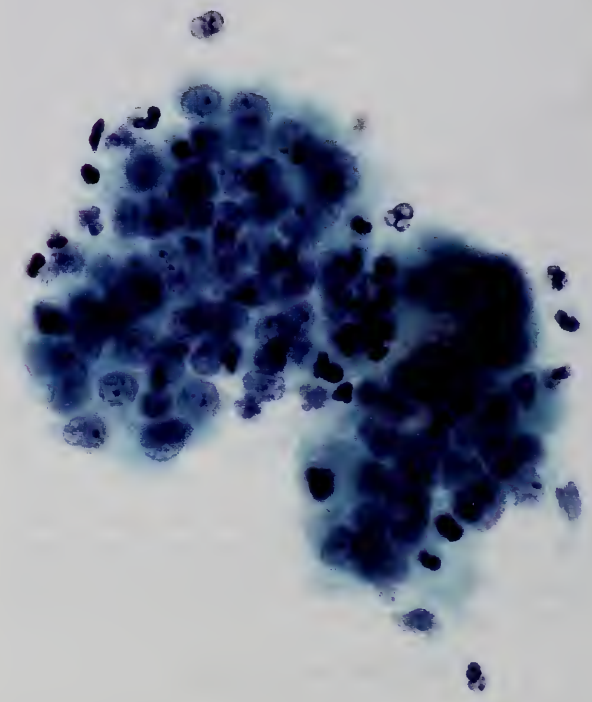


Figure 5-69

ATYPICAL GLANDULAR CELLS (REACTIVE ENDOCERVICAL GLANDULAR ATYPIA)

Left: Conventional cytologic preparation demonstrates an aggregate of endocervical cells with enlarged hyperchromatic to vesicular nuclei and small nucleoli accompanied by inflammatory cells (high-risk HPV DNA negative).

Right: Liquid-based cytologic preparation demonstrates an aggregate of endocervical cells with vesicular nuclei and small nucleoli (high-risk HPV DNA negative).

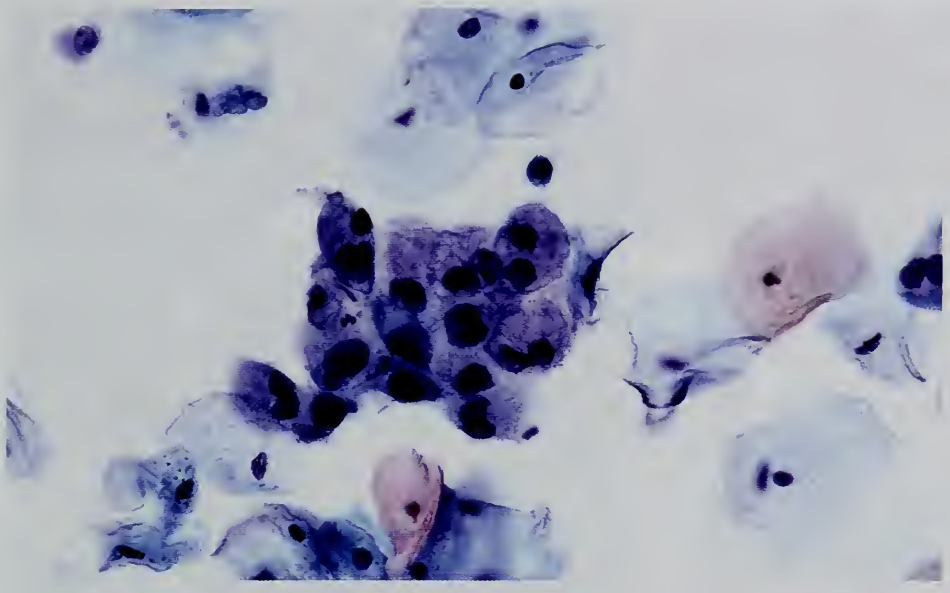


Figure 5-70

ATYPICAL GLANDULAR CELLS (REACTIVE/DEGENERATIVE ENDOCERVICAL GLANDULAR ATYPIA)

Cytologic preparation shows a group of endocervical cells with smudgy hyperchromatic nuclei.

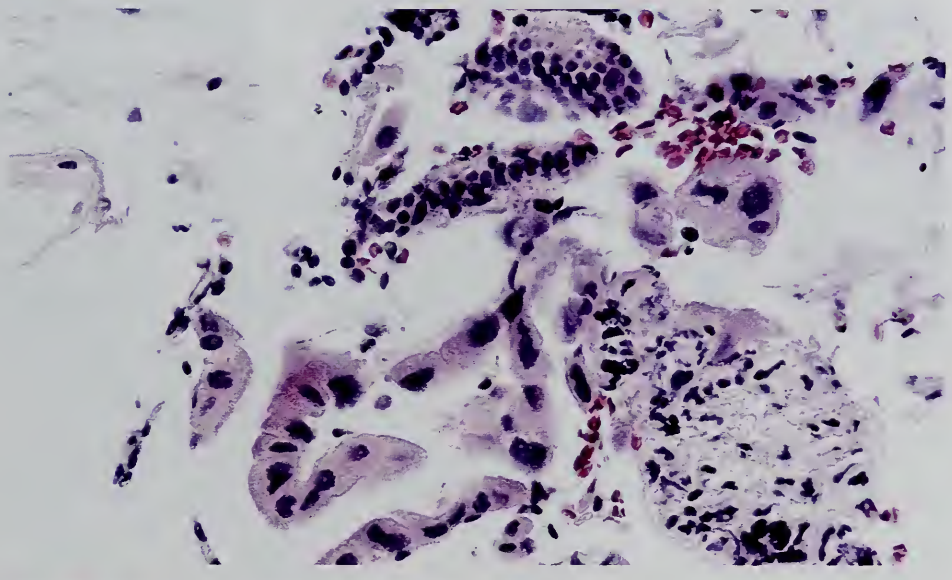


Figure 5-71

REACTIVE/DEGENERATIVE ENDOCERVICAL GLANDULAR ATYPIA

An endocervical curettage specimen corresponding to the cytologic preparation in figure 5-70 shows endocervical cells with smudgy hyperchromatic nuclei, without mitotic figures or apoptotic bodies.

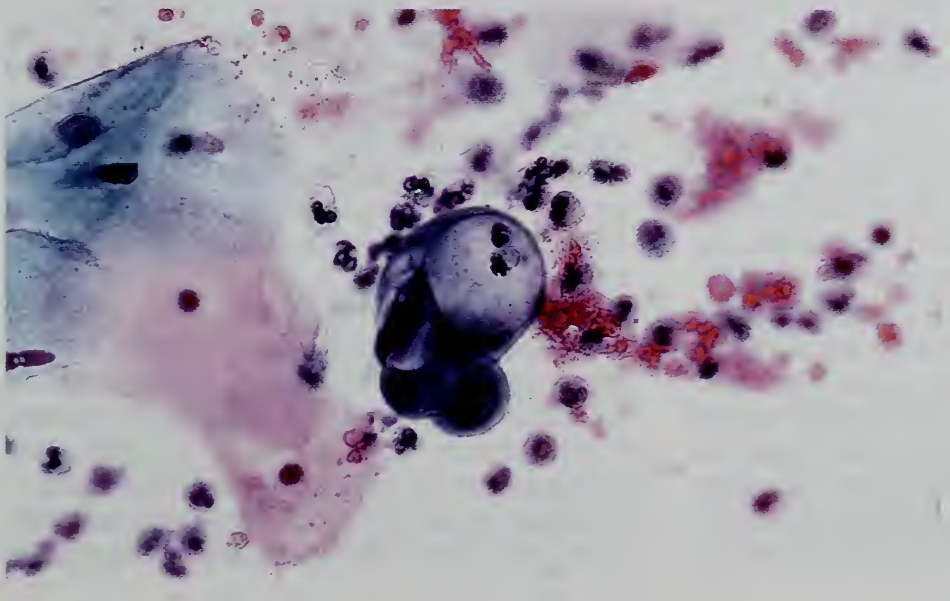


Figure 5-72

ATYPICAL GLANDULAR CELLS ASSOCIATED WITH INTRAUTERINE DEVICE USAGE

A cluster of glandular cells with some nuclear hyperchromasia and an intracytoplasmic vacuole suggests a glandular neoplasm.

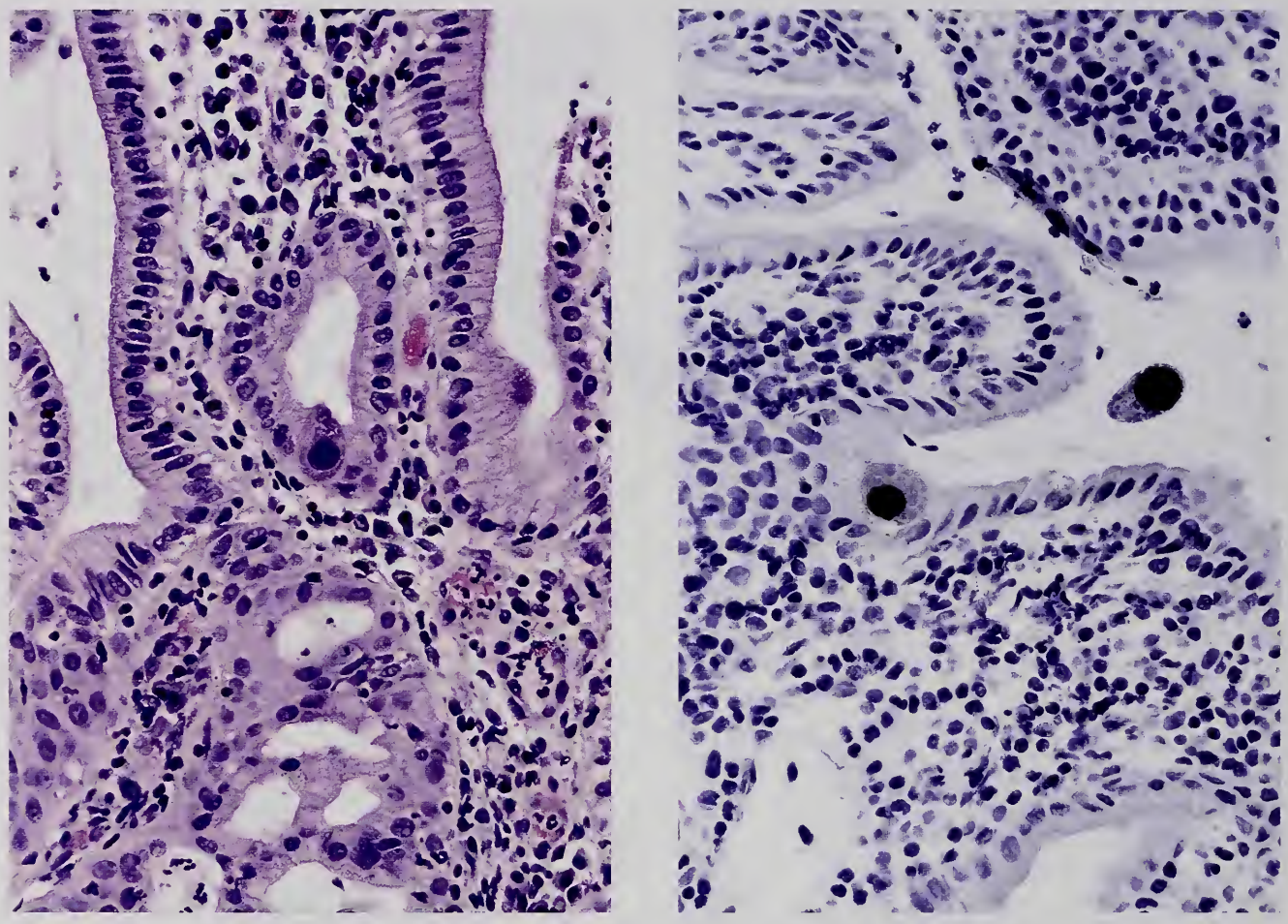


Figure 5-73

CYTOMEGALOVIRUS

Left: Intranuclear inclusions create nuclear enlargement that can simulate glandular atypia.
Right: Immunohistochemical stain for cytomegalovirus (CMV) confirms the diagnosis of the inclusions.

neoplasia, low-grade have been suggested for lesions with less atypia than adenocarcinoma in situ. However, specific, reproducible diagnostic criteria have not been established and thus these diagnostic terms are not recommended currently for use in practice.

Studies evaluating these so-called glandular dysplasias have thus far not found HPV within the lesions, leading some to doubt that they represent a precursor of adenocarcinoma in situ (236,399). A recognizable HPV-related glandular lesion with less atypia than adenocarcinoma in situ cannot exist because endocervical glandular epithelium does not undergo a maturation process as does squamous epithelium and does not develop cytologic changes related to productive HPV infection as seen in the maturing infected squamous cells of LSILs, precluding the development of an analogous low-grade form of glandular dysplasia (389). The presence of just increased mitotic activity, without accompanying nuclear atypia or apoptotic bodies, should not lead to a diagnosis of glandular atypia or adenocarcinoma in situ because this feature is encountered on occasion as an isolated finding in otherwise normal endocervical glands. In other cases, well-differentiated mucinous glands having some features of adenocarcinoma in situ but not as fully developed as in more readily recognized examples (see below), may actually represent an early well-differentiated form of adenocarcinoma in situ, particularly when there is a coexistent SIL and/or high-risk HPV infection present as determined by HPV testing. A scoring system has been proposed for quantitatively and qualitatively assessing the cytologic

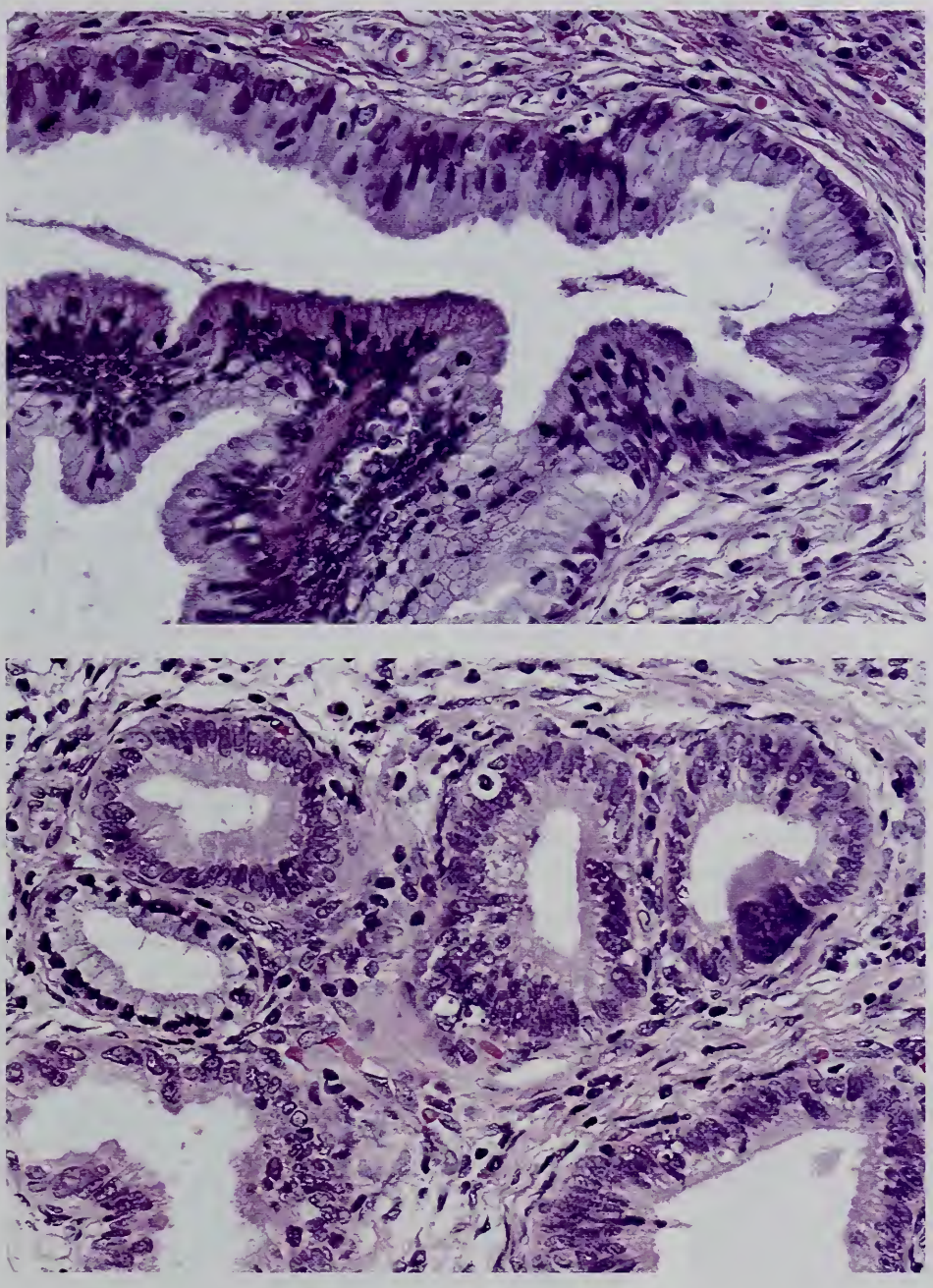


Figure 5-74

ENDOCERVICAL GLANDULAR ATYPIA

Top: Some endocervical glandular cells have enlarged nuclei. Several mitotic figures are present but the constellation of changes is insufficient to establish a diagnosis of AIS.

Bottom: Most of the glandular cells have modest nuclear enlargement, with the exception of two cells with significantly enlarged nuclei. A few apoptotic bodies are present but mitotic figures are lacking and the constellation of changes is insufficient to establish a diagnosis of AIS (follow-up cone biopsy specimen was negative).

features (atypia, stratification, mitotic figures, and apoptotic bodies) of endocervical glandular lesions to improve diagnostic reproducibility for adenocarcinoma in situ (174).

Adenocarcinoma In Situ

Definition. *Adenocarcinoma in situ* (AIS) is characterized by the replacement of glandular epithelium by cytologically malignant epithelial cells.

General Features. AIS is much less common than SIL. In the United States, based on estimates from the Surveillance Epidemiology and End Results (SEER) population database between 1973 and 1995, the age-adjusted incidence rate for AIS was 0.61 cases/100,000 compared to 27.93 cases/100,000 for squamous carcinoma in situ (CIS) (SEER program, National Cancer Institute, 2004). Of all in situ cervical lesions in the SEER database, 99 percent were classified as squamous and 1 percent as glandular. In the National Cancer Institute ALTS trial (382), which intensively studied 5,000 women with ASCUS and LSIL, the frequency of AIS was less than 1/1,000.

The median age at diagnosis of women with AIS in a recent large series was 35 years

compared to 41 years for women with invasive adenocarcinoma, suggesting that the transit time may be shorter than previously thought (421). Unlike invasive squamous carcinoma, in which the precursor lesion (CIS) is much more common than the carcinoma, the incidence of invasive adenocarcinoma is much higher than AIS in all age groups (321). A reason that has been suggested to account for this finding is that AIS is more difficult to detect cytologically and colposcopically than SIL and indeed, few women with invasive adenocarcinoma are identified through screening (292).

It is now well accepted that AIS is a precursor of invasive adenocarcinoma. Some of the strongest evidence comes from studies in which cytologic or histologic evidence of AIS was present several years before the detection of invasive adenocarcinoma (44,45).

AIS is found in association with SIL in 24 to 75 percent of cases (96). Patients with glandular and squamous lesions share many of the same risk factors including multiple sexual partners, use of oral contraceptives, and early onset of sexual activity (380,410). Moreover, high-risk HPV types, particularly HPV 18, have been detected in as many as 89 percent of cases (106).

Clinical Features. The vast majority of women diagnosed with AIS are asymptomatic. The lesions are detected either during cytologic screening or fortuitously on a biopsy or endocervical curettage as part of the workup of SIL. In women who are symptomatic, the most common symptom is vaginal bleeding, occurring in up to 60 percent of the patients (40), but discharge may be present as well (167).

Gross Findings. AIS has no distinctive gross appearance (66). Although in 65 percent of cases, the transformation zone is involved, AIS often lies outside the transformation zone, and therefore may not be visible colposcopically (308). When it is visible, the epithelium appears only slightly thicker, with the crypts more irregular than normal. AIS is usually unifocal but may be multifocal (16,39,77,308). It can extend as far as 3 cm into the endocervical canal.

Microscopic Findings. AIS consists of glands lined by cytologically malignant cells. The glands of AIS do not extend below the level of normal glands. AIS spreads along the surface of the endocervix without infiltrating the stroma and producing the desmoplasia characteristic of invasive carcinoma. Endocervical, intestinal, and endometrioid types of AIS have been reported (136,183). In addition, rare examples of adenosquamous carcinoma in situ (385) and clear cell carcinoma in situ (161) have been described.

The most common form of AIS is the *endocervical type*, in which the cells resemble those of the endocervix, with basal nuclei and pale granular mucinous cytoplasm. There is nuclear enlargement, hyperchromasia and coarsening of the chromatin, prominent mitotic activity including abnormal mitotic figures, and increased density of the cells lining the glands. Apoptosis is nearly always present (42). The increased mitotic figures and apoptotic bodies are among the most reliable diagnostic criteria. Typically, there is a sharp demarcation of AIS from nearby uninvolved glands and from the uninvolved epithelium of the same gland (figs. 5-75–5-77).

AIS of the *intestinal type* is characterized by the presence of goblet cells; argyrophilic cells may also be present (182). Typically, nuclear atypia is not as evident in the intestinal type because the mucin globules compress the nuclei toward the basal aspects of the cells, thereby reducing the degree of nuclear enlargement and pseudostratification (figs. 5-78, 5-79, 5-90).

Endometrioid AIS is characterized by glands resembling proliferative or hyperplastic endometrium, with scanty cytoplasm. The cytoplasm produces little or no mucin or has no goblet cells. Nuclear stratification is notable (figs. 5-80, 5-81) (39,45,116,135,183). The endocervical type can have variable amounts of mucinous cytoplasm, and typically exhibits some mucin depletion, imparting an appearance that is a hybrid of endocervical type mucinous and endometrioid differentiation. Thus, the distinction of these types is often arbitrary and primarily of academic interest. Endometrioid AIS is most distinctive when it exhibits a villoglandular architecture (fig. 5-81).

The *adenosquamous variant* is characterized by glands containing cells exhibiting both glandular and squamous features (fig. 5-82). This is in contrast to coexistent AIS and HSIL involving endocervical glands, in which individual glands contain cells having only glandular or squamous features (fig. 5-83).

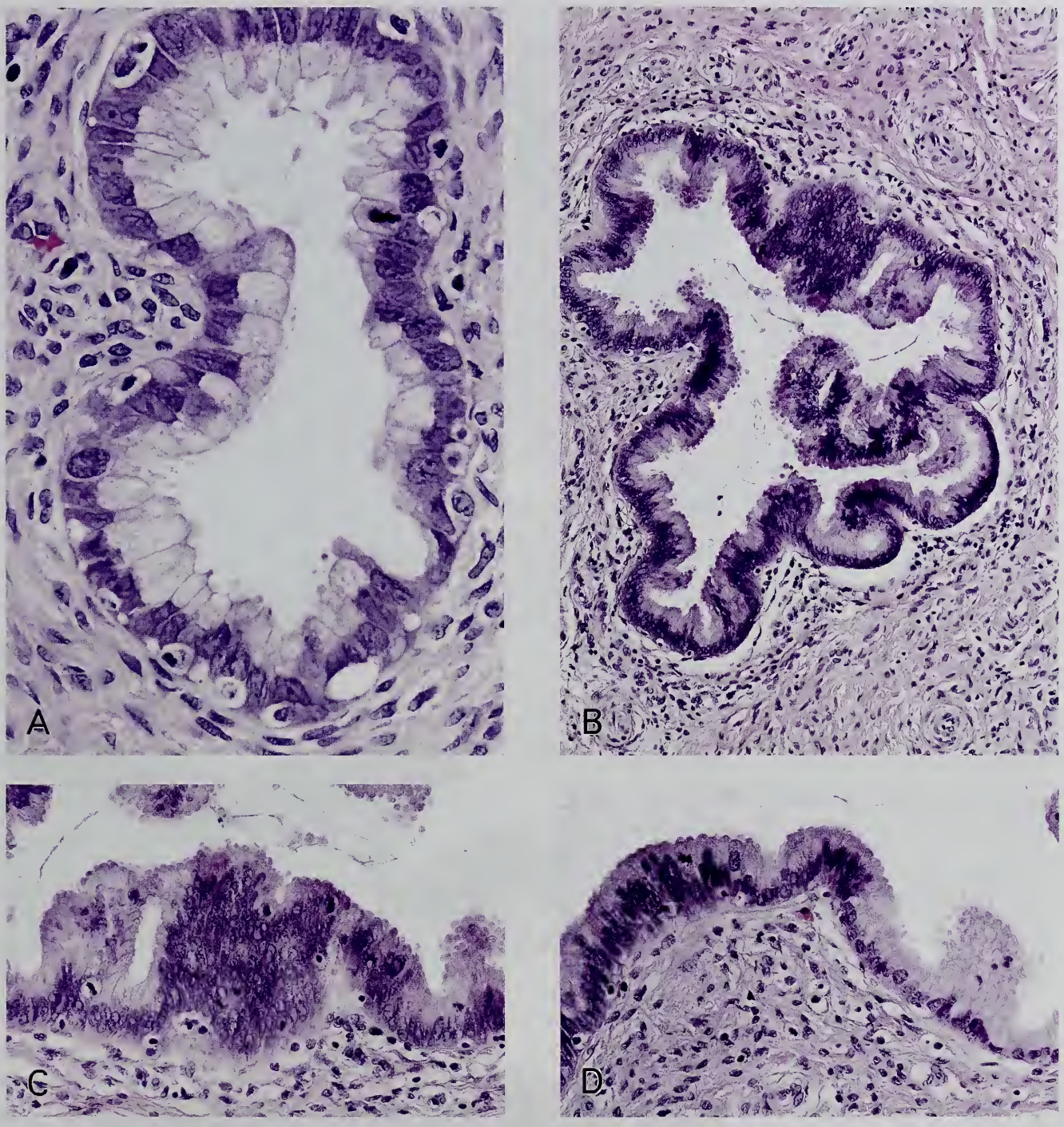


Figure 5-75

ENDOCERVICAL GLANDULAR ATYPIA, PROBABLY REPRESENTING ADENOCARCINOMA IN SITU

A: A single atypical gland is composed of cells that retain moderate amounts of mucinous cytoplasm but have uniformly enlarged nuclei. Several apoptotic bodies and a mitotic figure are present (follow-up cone biopsy specimen demonstrated AIS).

B: A single gland with a complex profile appears to have cells with greater nuclear enlargement and hyperchromasia than usually evident in normal endocervical glands at low magnification (see C; HSIL was present elsewhere in the specimen, indicating the presence of high-risk HPV).

C: Higher magnification shows that the epithelium is partially pseudostratified, nuclei are crowded and enlarged, and occasional mitotic figures and a few apoptotic bodies are present.

D: Nuclear atypia, one mitotic figure, and a few apoptotic bodies within a portion of an otherwise normal-appearing endocervical gland suggest AIS (only two glands in the cone biopsy specimen exhibited these focal changes; same case as illustrated in figure B).

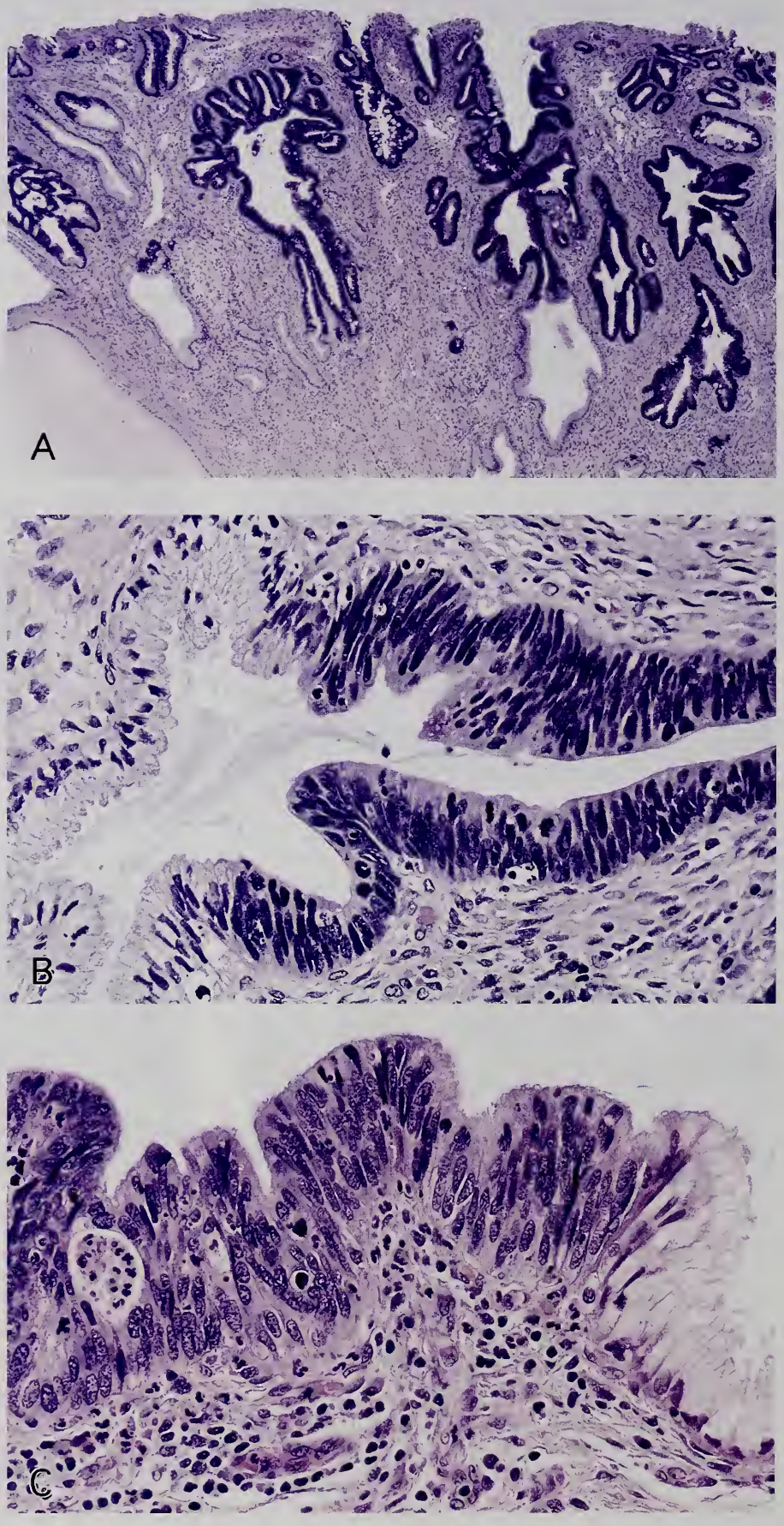


Figure 5-76

ADENOCARCINOMA IN SITU

A: Endocervical glands and crypts are either partially or completely lined by atypical epithelium but maintain their normal architectural pattern, indicating an in situ lesion.

B: There is an abrupt transition between normal and atypical endocervical glandular epithelium. Pseudostratified epithelium containing atypical, enlarged hyperchromatic nuclei, mitotic figures, and apoptotic bodies contrasts sharply with the normal endocervical glandular cells.

C: Abnormal nuclei are disordered and enlarged, and contain coarsely granular chromatin.

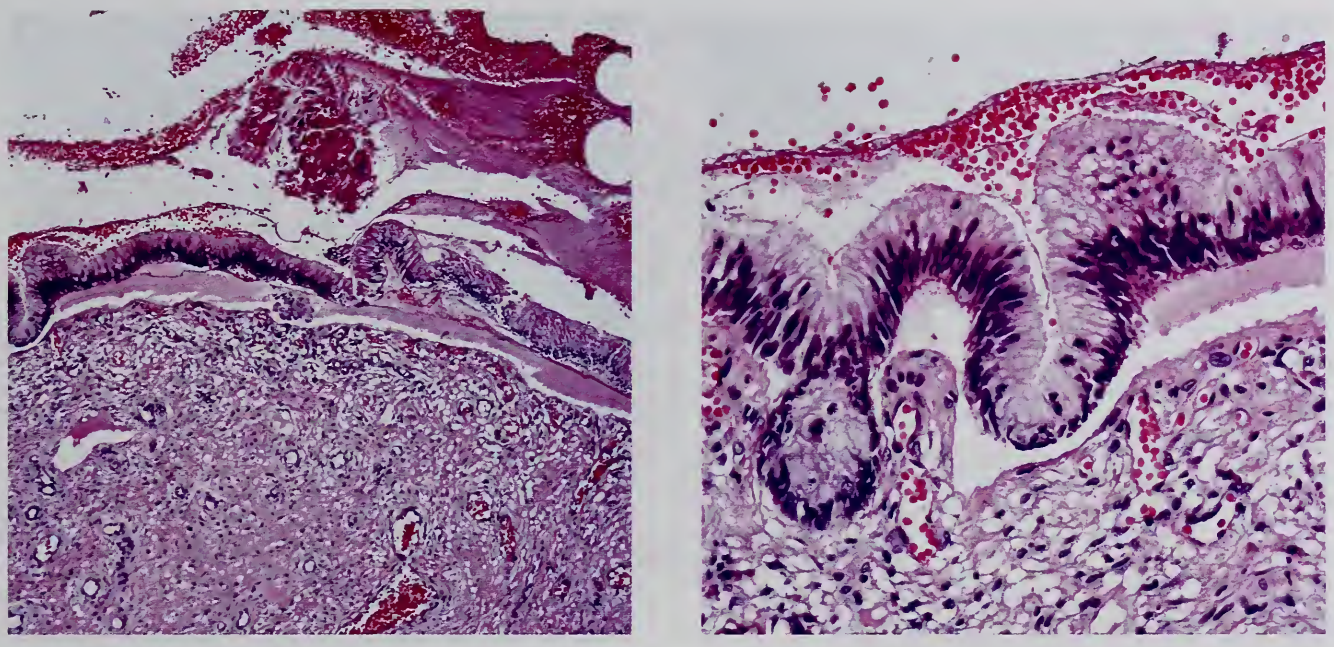


Figure 5-77

ADENOCARCINOMA IN SITU, SUPERFICIAL TYPE

Left: A single patch of atypical epithelium is present on the surface of the endocervical mucosa.
Right: Atypical epithelial cells retain moderate amounts of mucinous cytoplasm but nuclear atypia, mitotic figures, and apoptotic bodies are sufficient for a diagnosis of AIS.

Immunohistochemical and In Situ Hybridization Findings. AIS is characterized by diffuse, strong expression of p16, an elevated Ki-67 proliferation index, and frequent loss of hormone receptor expression (figs. 5-84, 5-85) (247,289,334,383,451). p16 expression is a surrogate marker for high-risk HPV infection in this setting and HPV can be demonstrated in the glandular epithelium by in situ hybridization (figs. 5-85, 5-86). In contrast, normal endocervical glands and most benign endocervical glandular proliferations express hormone receptors, exhibit only patchy and weaker expression of p16, and have low proliferation indices (334). CEA staining may be positive in AIS but is often absent and therefore not useful in the differential diagnosis. Immunostaining for p63, which is expressed in the basal and parabasal cells in LSIL and extends into the middle and upper layers in HSIL, is lacking in AIS (327).

Cytologic Findings. AIS is often identified in cytologic specimens as sheets, clusters, and strips of cells with nuclear crowding and overlap, without an accompanying tumor diathesis (66,287). Characteristic features of glandular differentiation include rosette formation, nuclear feathering, and palisading. Nuclear enlargement and diminished cytoplasm and mucin result in an increased nuclear-cytoplasmic ratio. Nuclear stratification, pleomorphism, and hyperchromasia with coarsely granular chromatin are also characteristic; the latter feature usually renders the nucleoli small and inconspicuous (figs. 5-86–5-90). These features can be modified in liquid-based preparations, with three-dimensional crowded cellular aggregates, more evident single atypical cells, less evident typical architectural features of glandular differentiation, and more open chromatin with more apparent nucleoli (fig. 5-88) (287). In nearly 30 percent of the cases, abnormal cells are not evident (308).

Differential Diagnosis. AIS must be distinguished from glandular hyperplasia, invasive adenocarcinoma, Arias-Stella reaction, glandular atypia due to inflammation or irradiation, microglandular hyperplasia, endometriosis, tubal metaplasia, and mesonephric remnants. Distinction of AIS from invasive adenocarcinoma can be difficult in the early phases of invasion. Invasion should be suspected if any of the following features is noted: loss of the lobulated architecture of AIS; stromal desmoplasia around

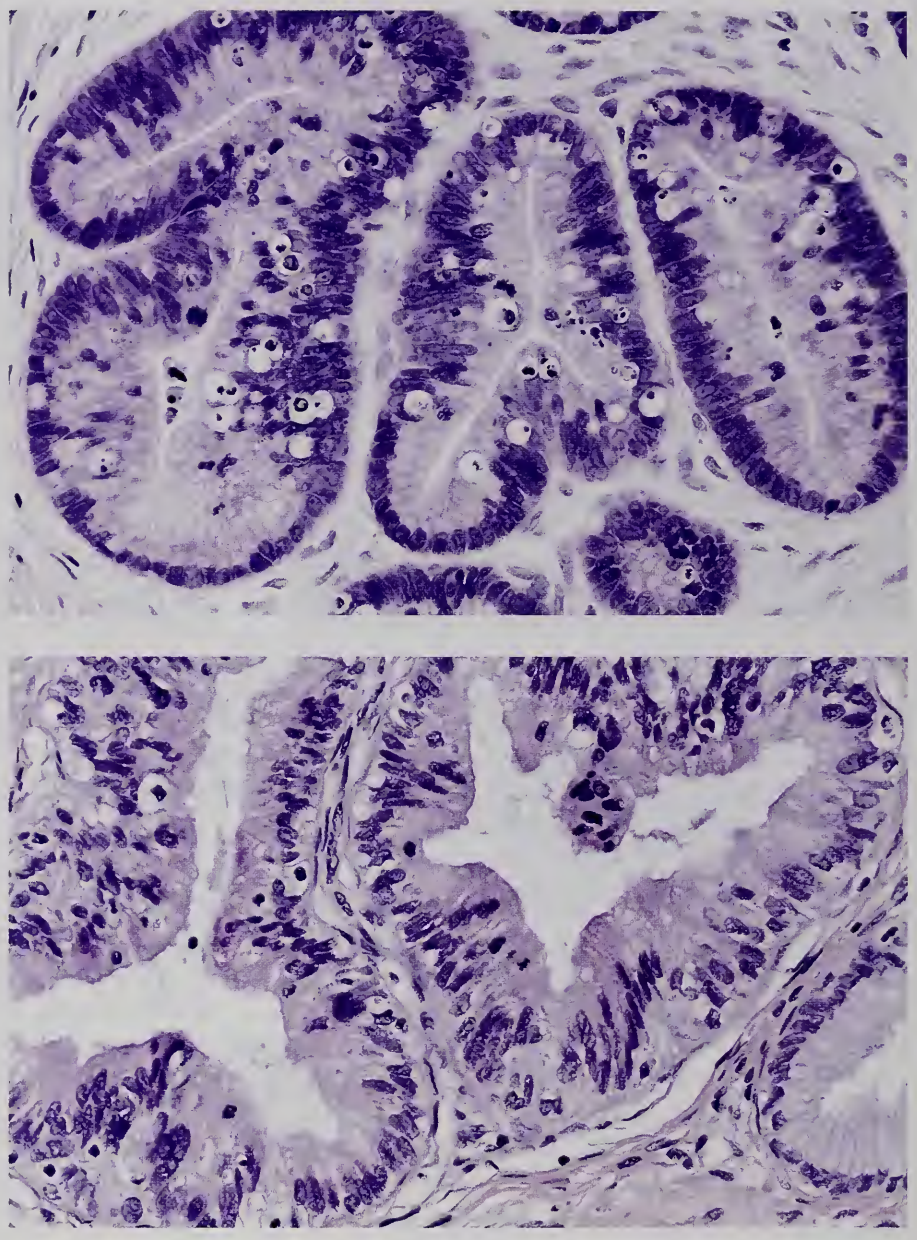


Figure 5-78

ADENOCARCINOMA IN SITU, USUAL TYPE WITH MUCINOUS DIFFERENTIATION

Top: Glandular cells have abundant apical mucinous cytoplasm. Numerous apoptotic bodies are present.

Bottom: Well-differentiated glands retain abundant mucinous cytoplasm but nuclear atypia, mitotic figures, and apoptotic bodies are sufficient for a diagnosis of AIS (compare to normal gland at edge).

the involved glands; exuberant glandular budding; abnormal glands extending beyond the depth of normal glands; abnormal glands arranged as aggregates of tightly clustered small glands; a confluent glandular, labyrinthine, or extensive papillary pattern; a cribriform pattern in confluent glands (rather than just within a single or isolated glands); or glands that are closely applied to or wrap around medium or large blood vessels (426,446). In well-differentiated forms, however, an inflammatory or desmoplastic response may not be present. Early invasion is most readily recognized when small nests of cells or individual cells bud from the AIS glands and project into the adjacent stroma or become detached from the AIS glands. These cells characteristically have increased amounts of eosinophilic cytoplasm and altered nuclear features compared with typical AIS. Specifically, in invasive carcinoma, nuclei contain vesicular chromatin with prominent nucleoli rather than the granular nuclear hyperchromasia obscuring nucleoli as occurs in AIS.

Discrimination of AIS from the Arias-Stella reaction in glands of the endocervix may pose a problem because the latter is characterized by markedly enlarged cells with hyperchromatic nuclei. In contrast to AIS, the Arias-Stella

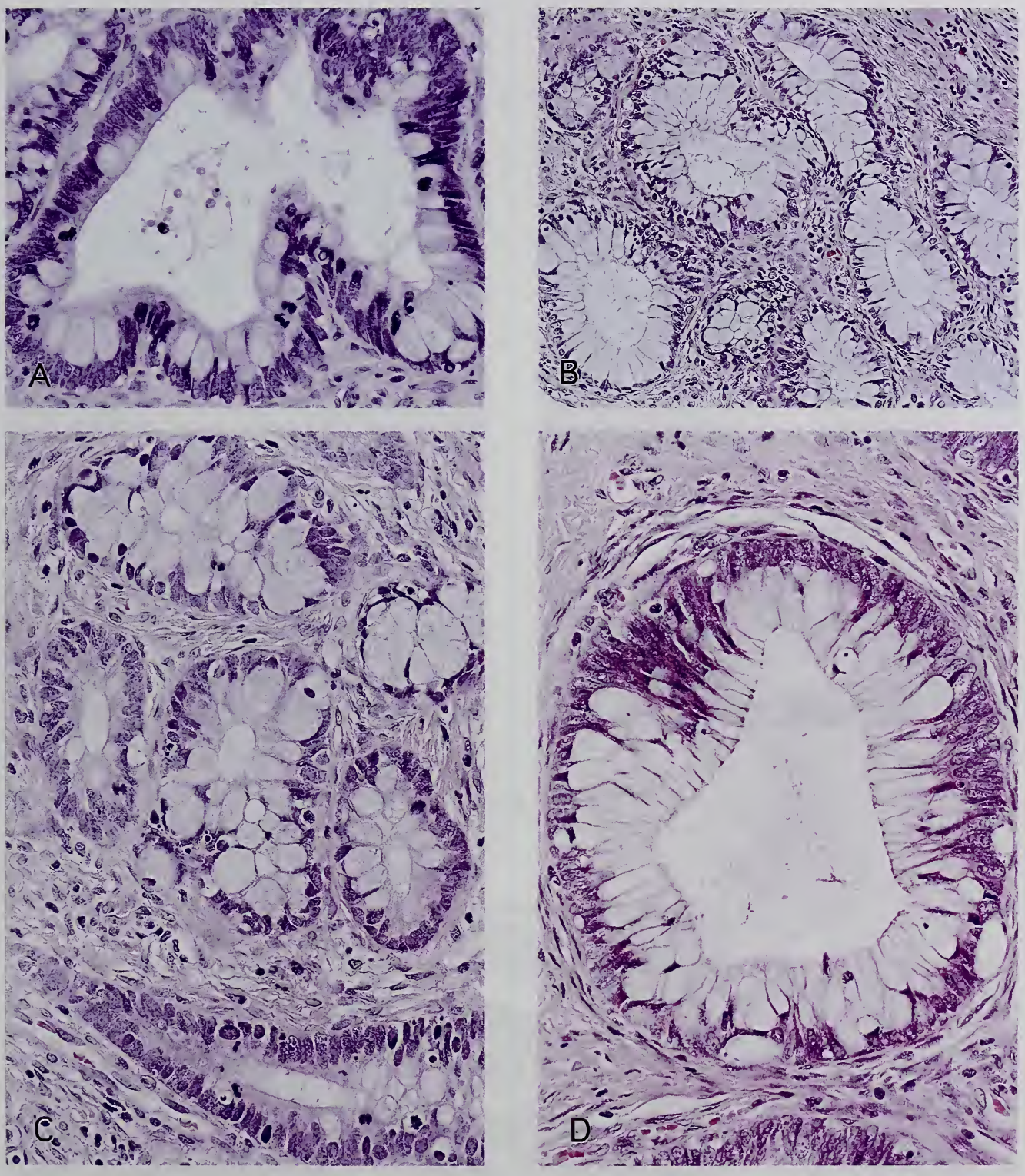


Figure 5-79

ADENOCARCINOMA IN SITU, INTESTINAL TYPE

A: Atypical glands have prominent mucinous differentiation with goblet cells.

B: Extensive goblet cell differentiation can mask nuclear enlargement and atypia by compressing the nuclei at the basal aspect of the cells.

C: Nuclear atypia and mitotic activity in portions of glands having less goblet cell differentiation assist in identifying the entire lesion as AIS.

D: Careful assessment of the nuclei discloses notable atypia despite compression by large mucinous goblets.

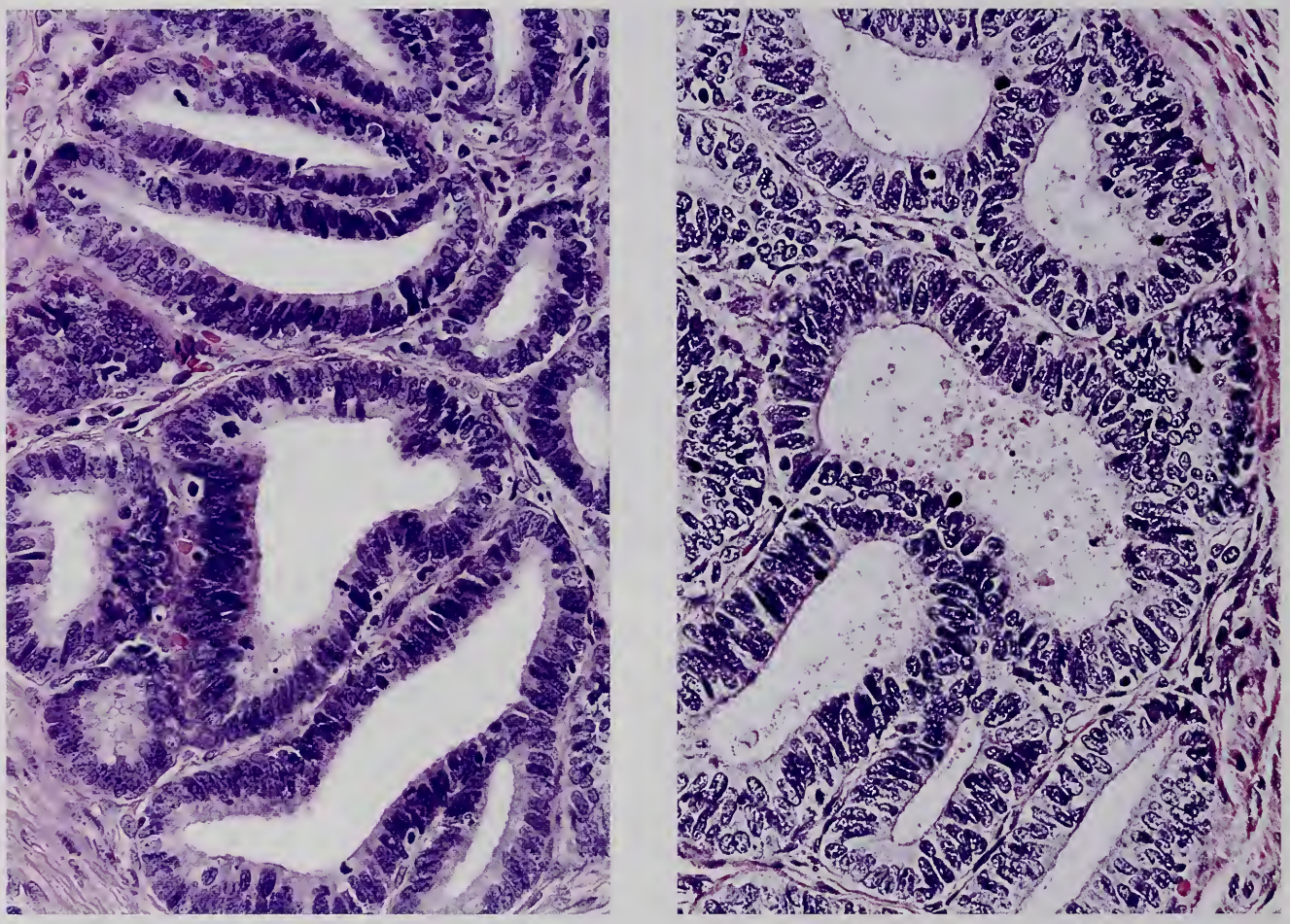


Figure 5-80

ADENOCARCINOMA IN SITU, ENDOMETRIOID TYPE

Cells have reduced amounts of mucinous cytoplasm and elongated hyperchromatic nuclei, imparting an "endometrioid" appearance.

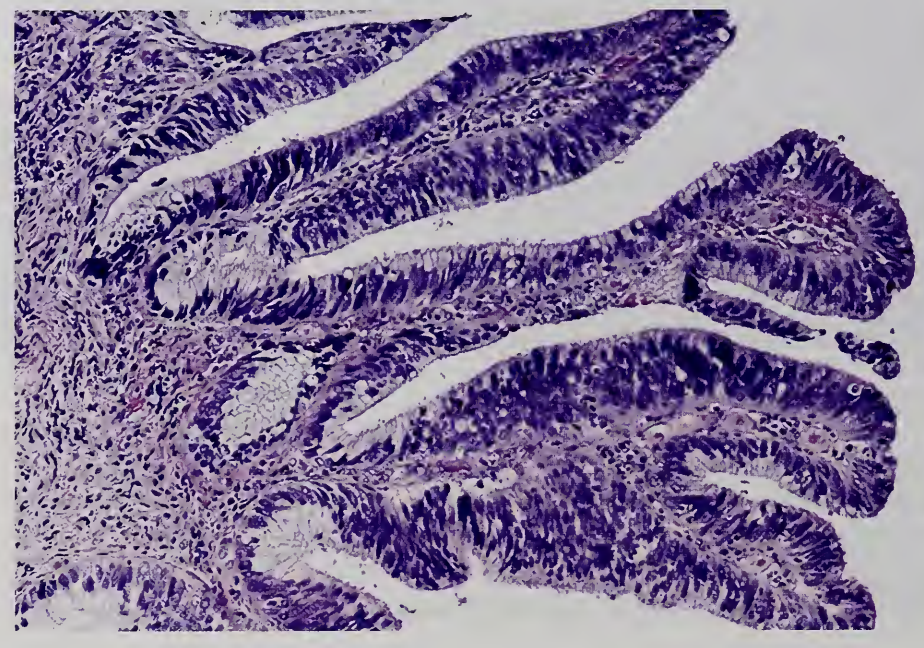
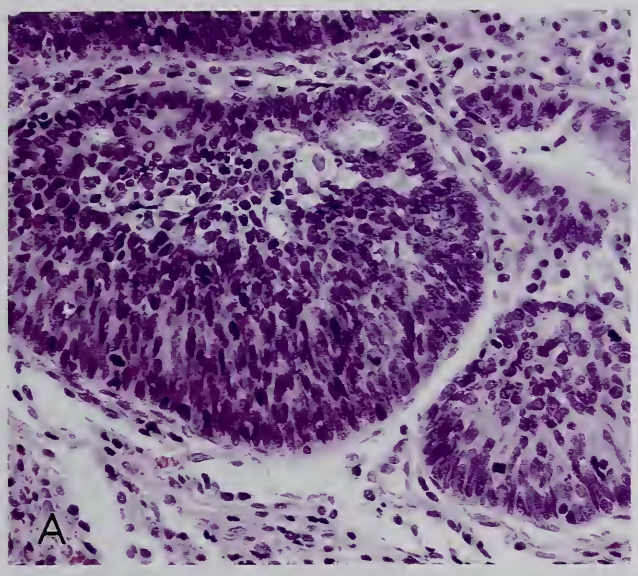
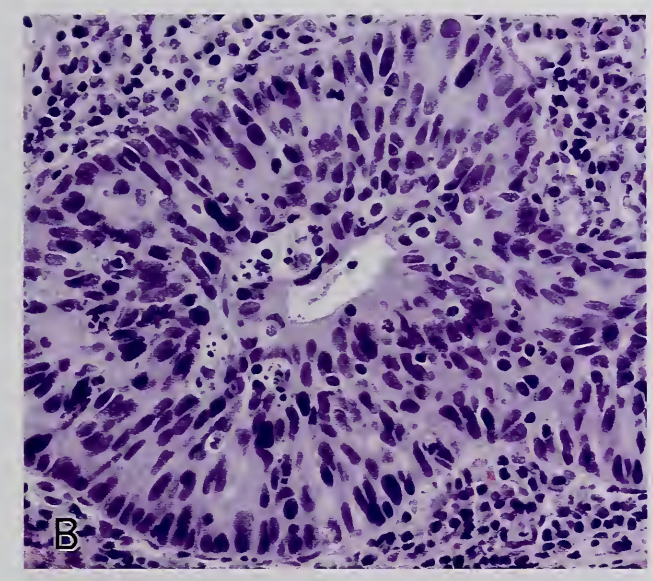


Figure 5-81

ADENOCARCINOMA IN SITU, VILLOGLANDULAR TYPE

Atypical surface epithelium forms elongated villiform structures.





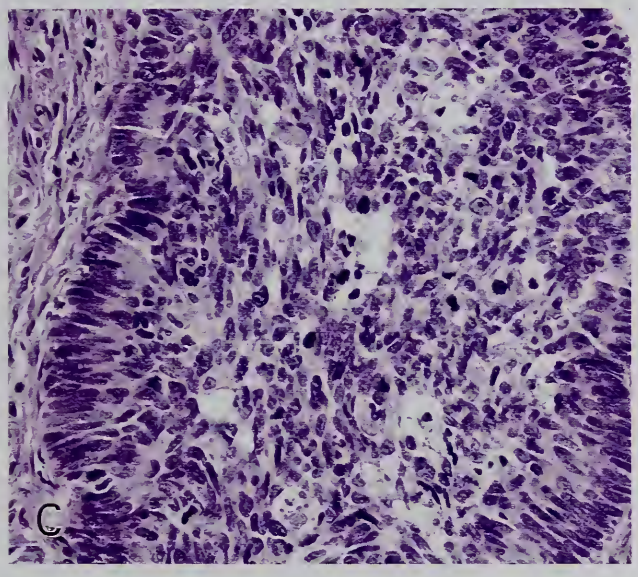


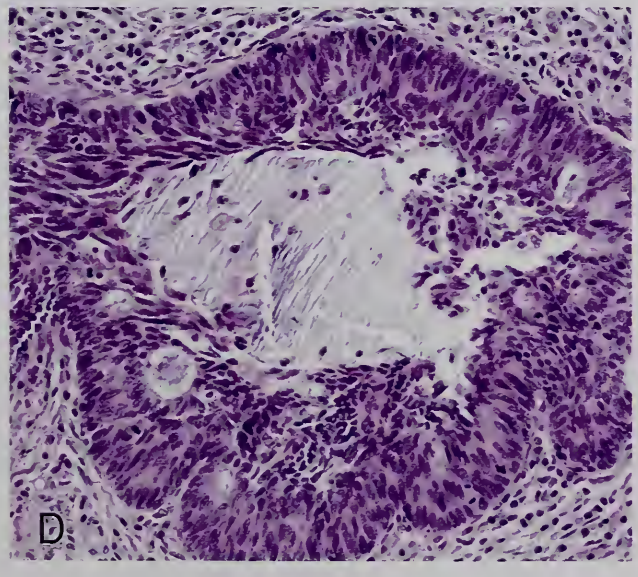
Figure 5-82

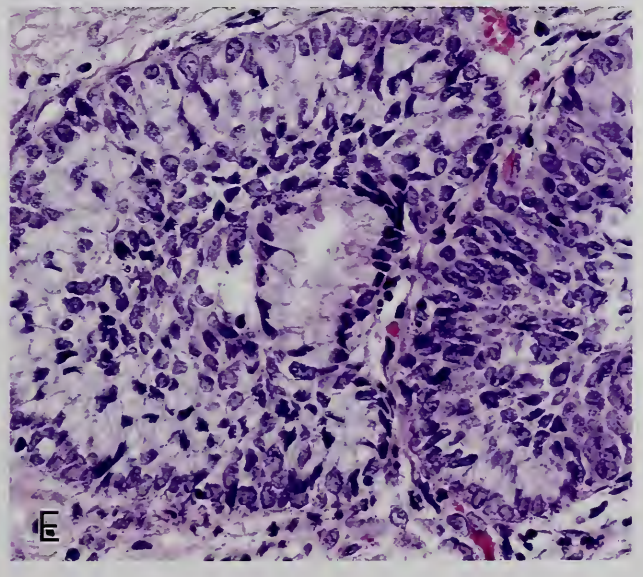
ADENOSQUAMOUS CARCINOMA IN SITU

A,B,C: Glands are lined and filled by atypical cells having both glandular and squamous features.

D: Small glandular lumens are present.

E: Atypical cells fill an endocervical gland and undermine the normal glandular epithelium. Multilayering of the epithelium is a squamous feature but many cells have mucinous cytoplasm, indicating glandular differentiation.





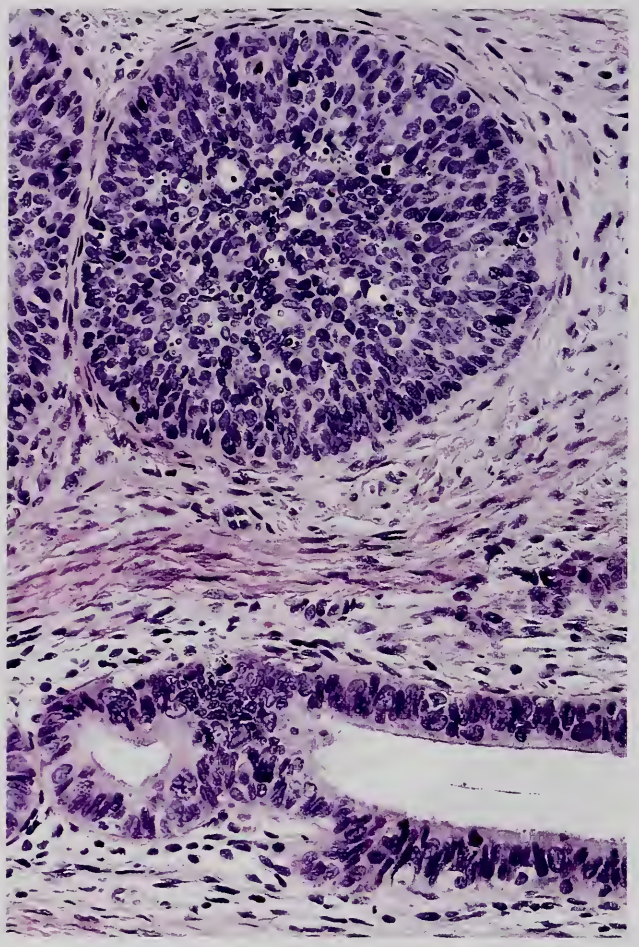


Figure 5-83

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION INVOLVING AN ENDOCERVICAL GLAND WITH ADJACENT ADENOCARCINOMA IN SITU

HSIL and AIS are morphologically discrete lesions with purely squamous features in the former and purely glandular features in the latter, whereas the glands involved by adenosquamous carcinoma in situ are lined by cells exhibiting a hybrid of glandular and squamous features (see fig. 5-82). Spaces created by apoptotic bodies simulate gland lumens within the HSIL.

reaction occurs in only sporadic areas in a gland or in glands that are tortuous and hypersecretory. The nuclei of the cells characteristically protrude into the lumen with little accompanying cytoplasm, displaying a "hobnail" appearance, and mitotic activity is rare.

Viral infections such as herpes and cytomegalovirus disease may result in nuclear enlargement. In contrast to the diffuse nature of the involvement by AIS, however, the affected cells are isolated and sporadic in cytomegalovirus infection and clustered in herpesvirus infection. Inflammation and focal ulceration are also prominent in herpes infections.

Glandular atypia can reflect a reactive/reparative response to inflammation or irradiation and is characterized by a single layer of epithelial cells showing nuclear enlargement, pleomorphism, and prominent nucleoli. Nuclear chromatin may be dark but is generally smudged and degenerative rather than coarsely granular as in AIS. The cytoplasm in glandular atypia tends to be granular and vacuolated, and mitotic figures are absent. Typically there is an associated acute and chronic inflammatory reaction, and polymorphonuclear leukocytes may infiltrate the epithelium. Atypia resulting from irradiation is characterized by glands lined by cuboidal or flattened epithelium with little or no stratification. Cells are generally large, with abundant cytoplasm, and nuclei are round to oval and vesicular, with prominent eosinophilic nucleoli. The nuclear-cytoplasmic ratio is generally unaltered due to similar concomitant increases in both the volume of cytoplasm and the nuclear size. Mitotic figures are not present (240). Glandular atypia has greater cellular pleomorphism than AIS.

Recently, it was reported that immunohistochemistry with the laminin-5 gamma2 chain facilitates the recognition of early invasion since cytoplasmic staining is detected at the leading edge of the areas of invasion and in tumor buds of AIS with minimal stromal invasion (290). Microglandular hyperplasia differs from AIS because it is often polypoid and characterized by a denser concentration of smaller, more uniform glands. The glands of microglandular hyperplasia are lined by vacuolated cells with uniform bland nuclei that lack mitotic activity. In contrast, AIS is not polypoid, has much more cytologic atypia and stratification, and the atypical cells occupy normally positioned glands. Unusual forms of microglandular hyperplasia may contain solid sheets of cells and include signet ring-like cells, but they are typically accompanied by characteristic features (439).

Endometriosis is characterized by glands lined by endometrial type cells with basally oriented nuclei lacking atypia. There may be cellular stratification and mitotic activity but the lack of atypia, presence of endometrial type stroma, and occasional presence of ciliated cells distinguish endometriosis from AIS.

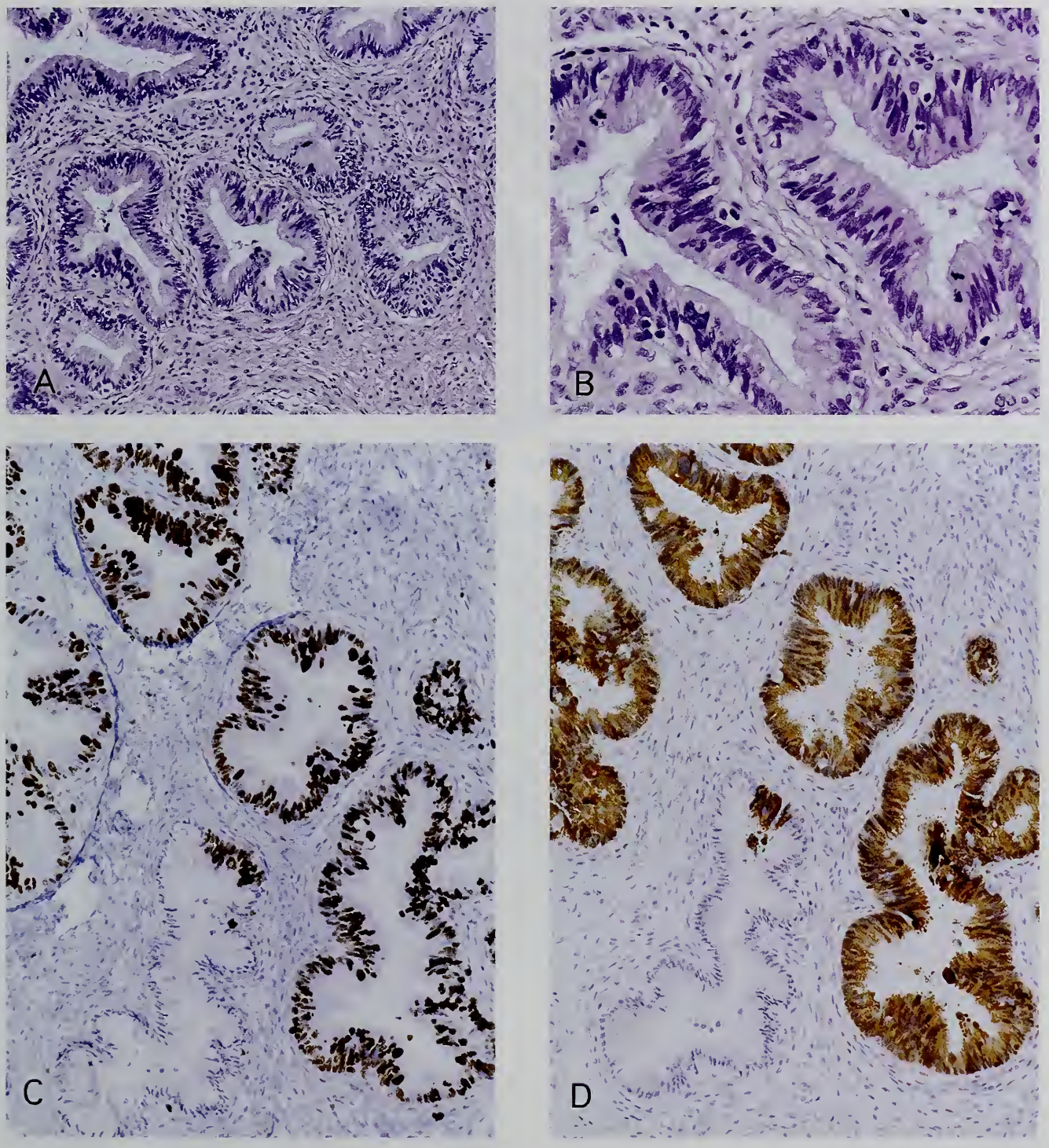


Figure 5-84

ADENOCARCINOMA IN SITU

A: Well-differentiated mucinous type of AIS appears only modestly more atypical than the adjacent normal endocervical gland at low magnification but cytologic and immunohistochemical features confirm the diagnosis (B–D).

B: Higher magnification of the lesion reveals the requisite cytologic features of AIS.

C: Immunohistochemical stain for Ki-67 demonstrates that the glands of AIS have a significantly increased proliferation index compared with normal glands. A gland partially involved by AIS shows increased proliferative activity only within the lesional portion.

D: Immunohistochemical stain for p16 demonstrates diffuse expression in the glands completely involved by AIS. A gland partially involved by AIS shows p16 expression only within the lesional portion.

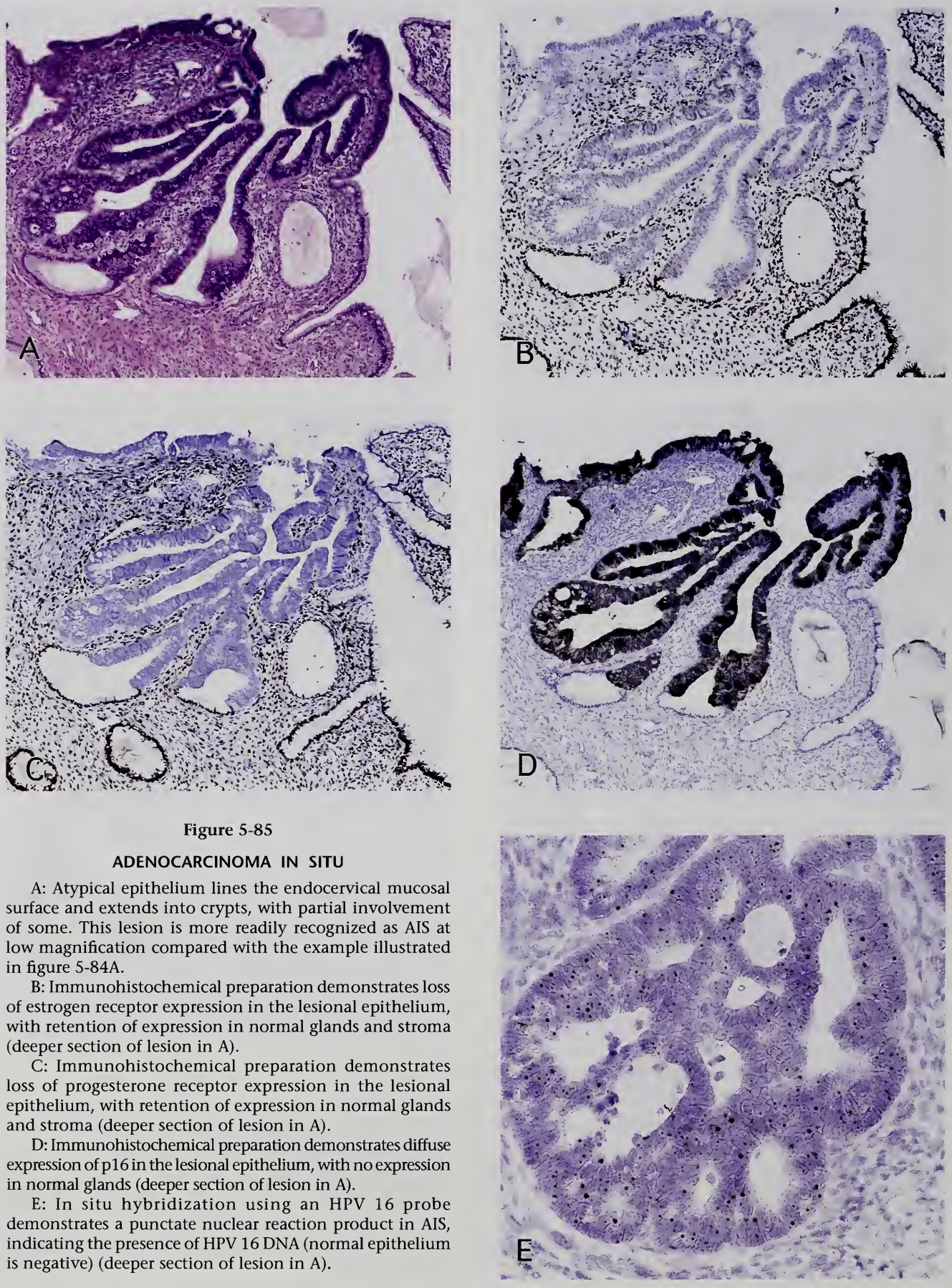


Figure 5-85

ADENOCARCINOMA IN SITU

A: Atypical epithelium lines the endocervical mucosal surface and extends into crypts, with partial involvement of some. This lesion is more readily recognized as AIS at low magnification compared with the example illustrated in figure 5-84A.

B: Immunohistochemical preparation demonstrates loss of estrogen receptor expression in the lesional epithelium, with retention of expression in normal glands and stroma (deeper section of lesion in A).

C: Immunohistochemical preparation demonstrates loss of progesterone receptor expression in the lesional epithelium, with retention of expression in normal glands and stroma (deeper section of lesion in A).

D: Immunohistochemical preparation demonstrates diffuse expression of p16 in the lesional epithelium, with no expression in normal glands (deeper section of lesion in A).

E: In situ hybridization using an HPV 16 probe demonstrates a punctate nuclear reaction product in AIS, indicating the presence of HPV 16 DNA (normal epithelium is negative) (deeper section of lesion in A).

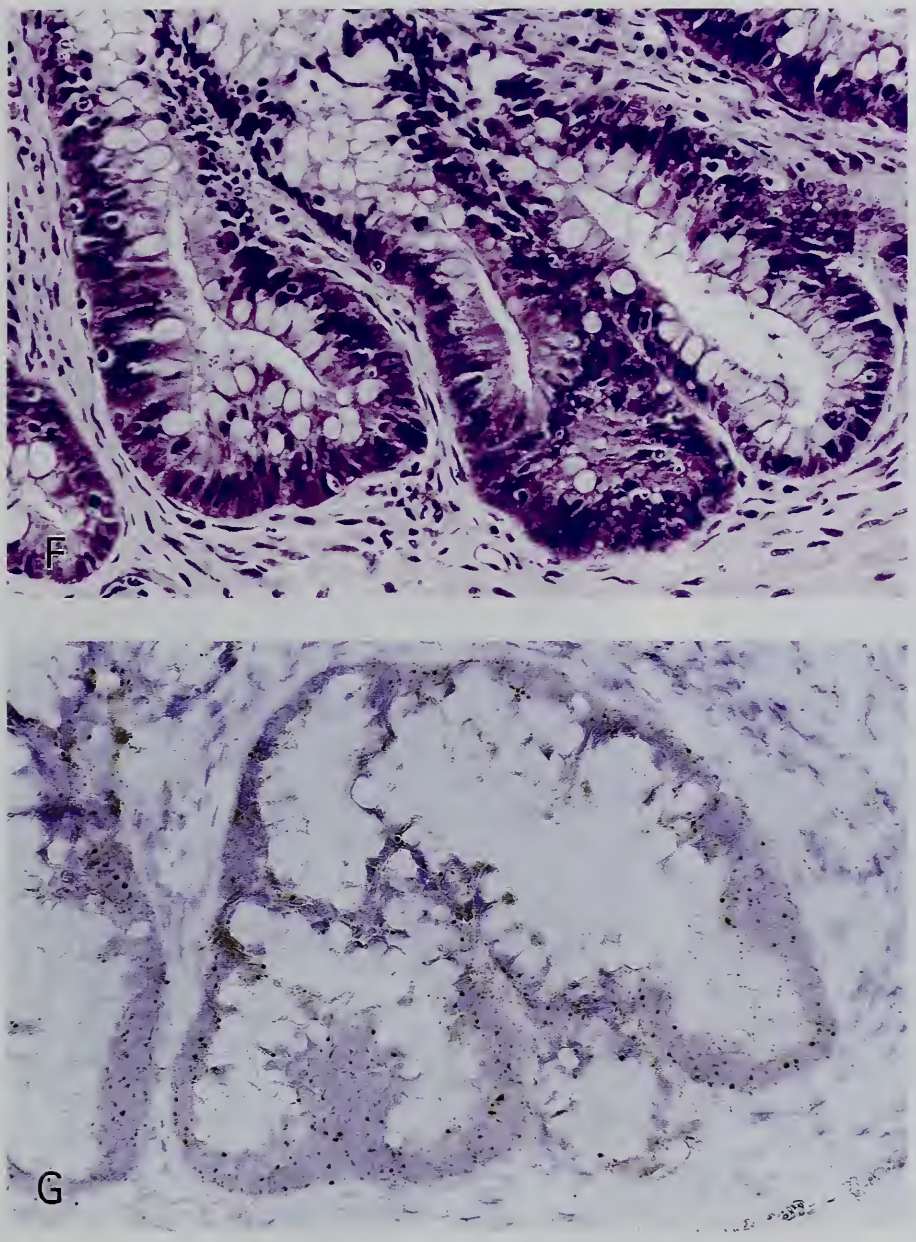


Figure 5-85 (continued)

F: Intestinal type AIS exhibits goblet cell differentiation. This lesion was associated with small cell carcinoma, which has an association with HPV 18.

G: In situ hybridization using an HPV 18 probe demonstrates punctate nuclear signals, indicating the presence of HPV 18 DNA in the lesion illustrated in F (positive signals were also present in the associated small cell carcinoma; see fig. 5-126.

Tubal metaplasia can be confused with AIS but the epithelium in tubal metaplasia lacks significant nuclear atypia and contains several different cell types, including ciliated cells (see section on tubal metaplasia). Atypical tubal metaplasia has been described, in some cases adjacent to AIS, suggesting that it may be related to AIS (356). The glands contain ciliated cells and otherwise resemble tubal metaplasia but notable nuclear atypia is present. The behavior of atypical tubal metaplasia is not well understood and such lesions should, for the moment, be carefully evaluated for the presence of coexistent AIS.

Mesonephric remnants, in contrast to AIS, are usually located deep in the stroma, although they occasionally impinge on normal endocervical glands near the mucosal surface. The glands lack the columnar morphology, atypical nuclear features, and mitotic activity seen in AIS.

Immunostains for p16, Ki-67, and hormone receptors are useful in distinguishing AIS from the benign lesions in the differential diagnosis. The benign lesions listed above are generally characterized by expression of hormone receptors, negative or patchy staining for p16, and low proliferation indices.

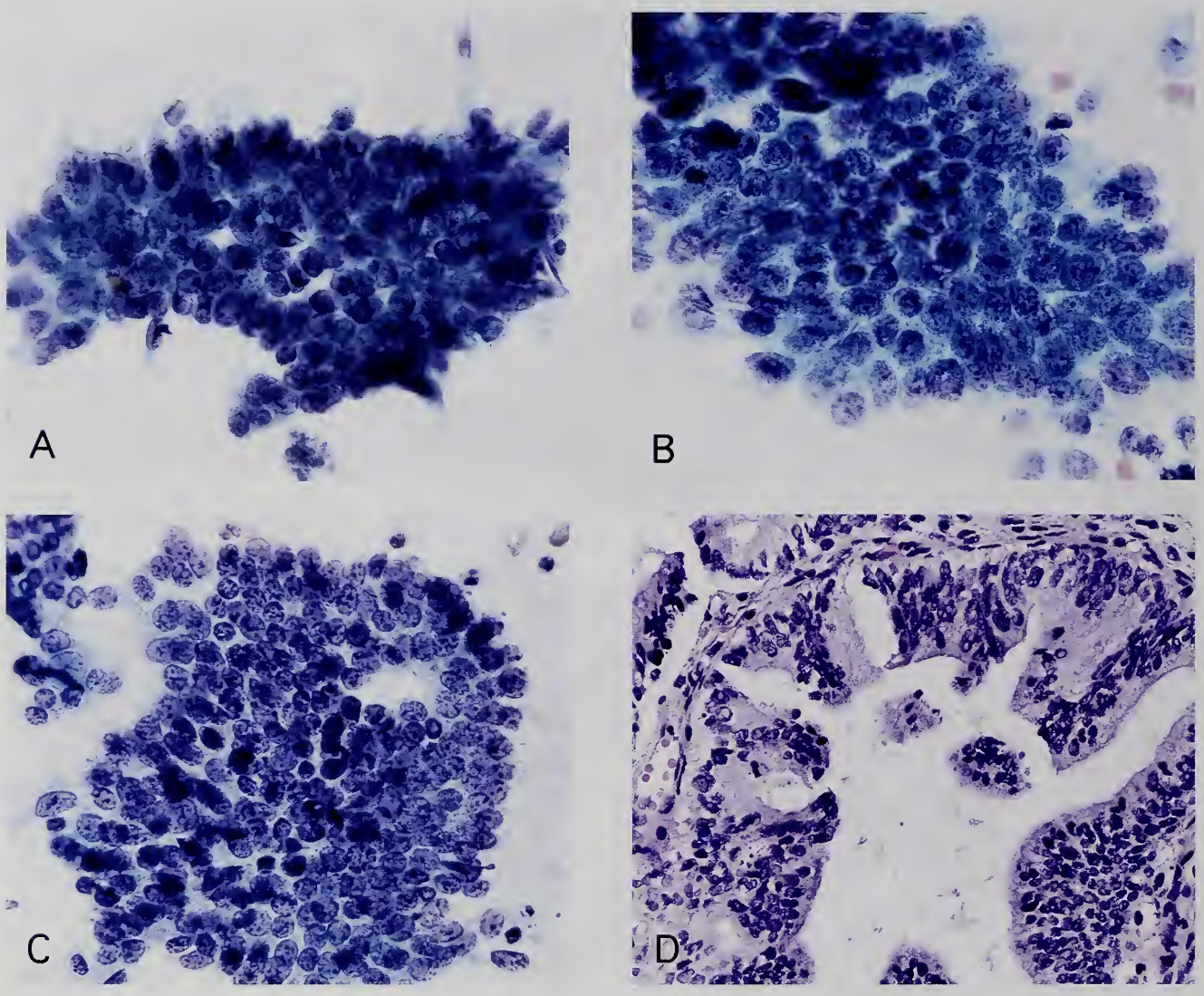


Figure 5-86

ADENOCARCINOMA IN SITU

A: An aggregate of crowded endocervical cells demonstrates nuclear enlargement, nuclear hyperchromasia with granular chromatin, rosette formation, and peripheral palisading ("feathering") of nuclei.

B: A sheet of endocervical epithelial cells contains crowded enlarged nuclei with granular chromatin and evident nucleoli.

C: Endocervical epithelial cells have crowded, enlarged, hyperchromatic nuclei and focal rosette formation.

D: A biopsy specimen corresponding to the cytologic preparations illustrated in figures A–C shows endocervical glandular epithelial cells with hyperchromatic, atypical, pseudostratified nuclei and mitotic activity, confirming the cytologic diagnosis of AIS.

Treatment and Prognosis. AIS is treated either by conization or hysterectomy. Relapse occurs more frequently after conization than hysterectomy, perhaps due to the multifocal distribution of AIS. In young women who are desirous of retaining fertility, cervical conization is recommended. Some studies have reported no residual disease in subsequent hysterectomy specimens and evidence of recurrence if the cone margins are clear (370) whereas others have reported residual disease in up to 40 percent of cases (24). In a review of the literature, recurrent disease was reported in 14 percent of cases with clear margins and 50 percent if the margins were involved (105). Nearly all investigators recommend cytologic and colposcopic follow-up; however, these tests are poor in detecting lesions initially and thus probably also in follow-up. Follow-up using HPV testing has been reported to be superior to margin status

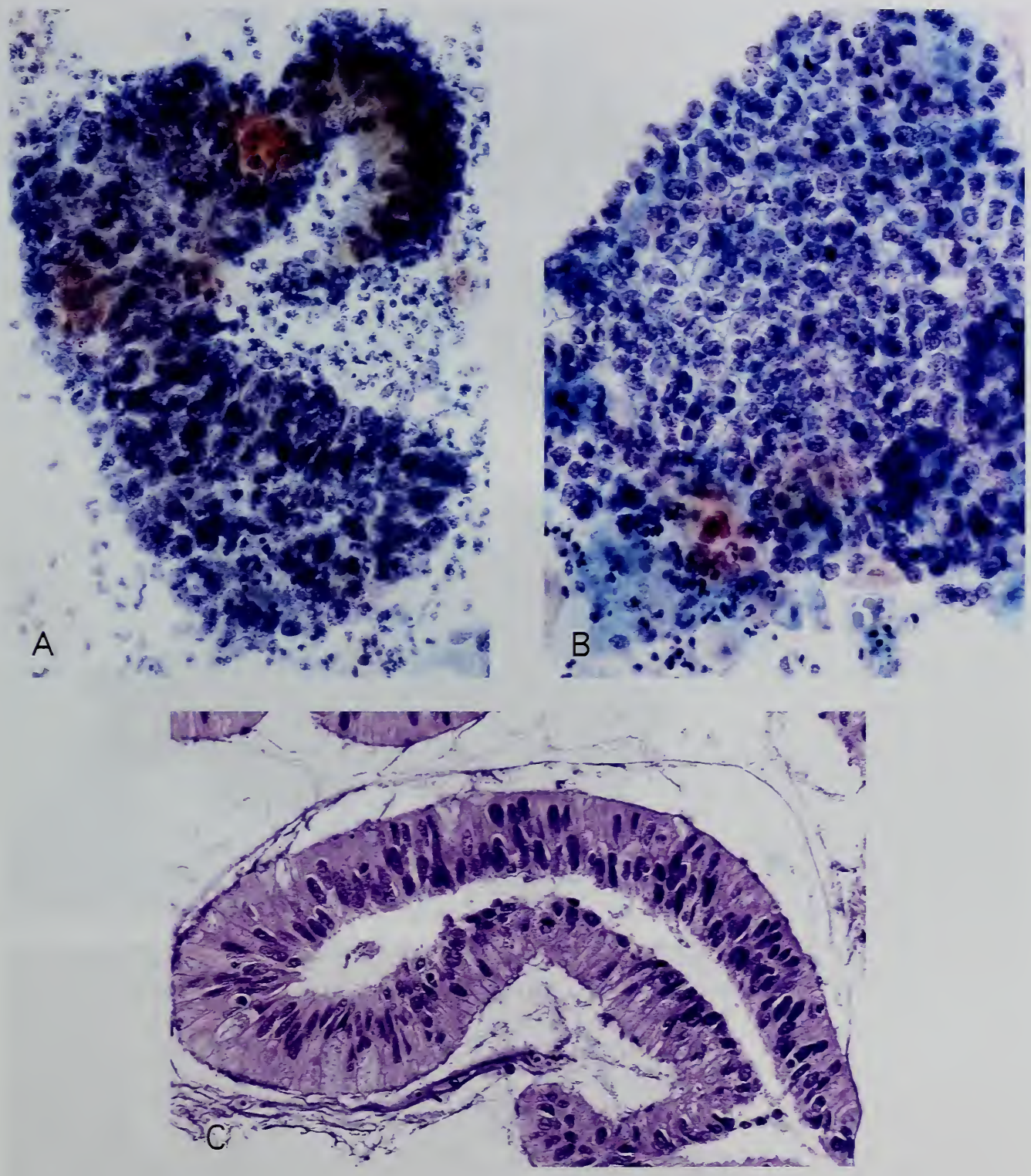


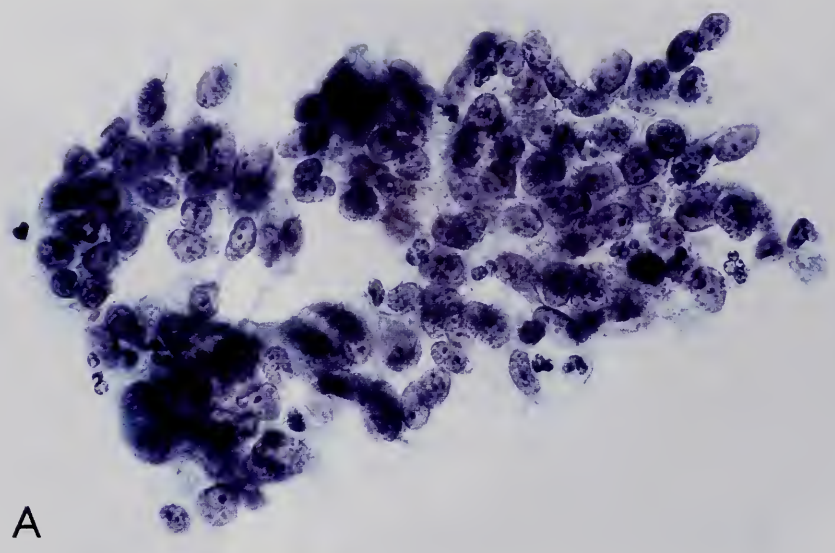
Figure 5-87

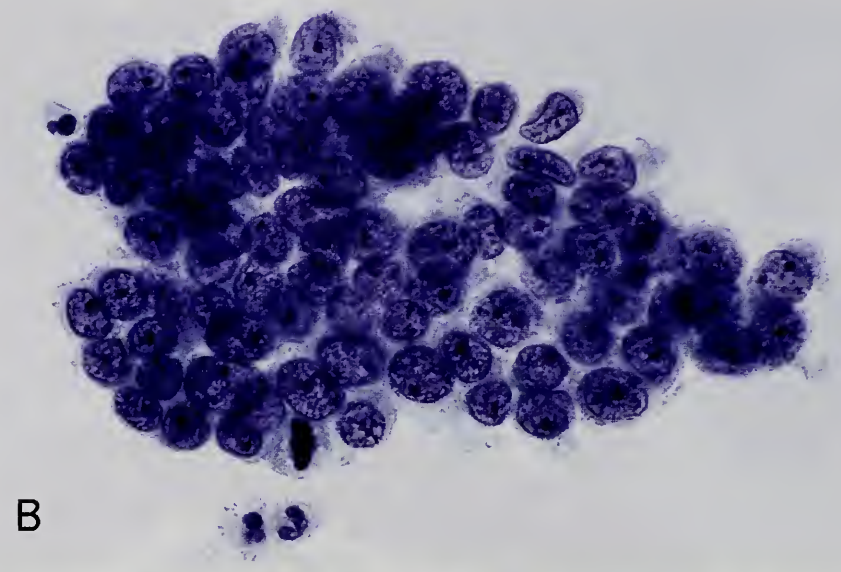
ADENOCARCINOMA IN SITU

A: A fragment of atypical endocervical epithelium in a cytologic smear shows both the en face (honeycomb) and in profile (palisaded) appearance of the crowded, enlarged hyperchromatic nuclei of AIS.

B: Atypical endocervical epithelium has a crowded honeycomb appearance in a liquid-based cytologic preparation but nuclei are less hyperchromatic and nucleoli are more evident than in a conventional smear (same case as A).

C: Biopsy specimen corresponding to the cytologic preparations illustrated in A and B demonstrates endocervical glandular epithelial cells with hyperchromatic atypical nuclei and mitotic activity, confirming the cytologic diagnosis of AIS.





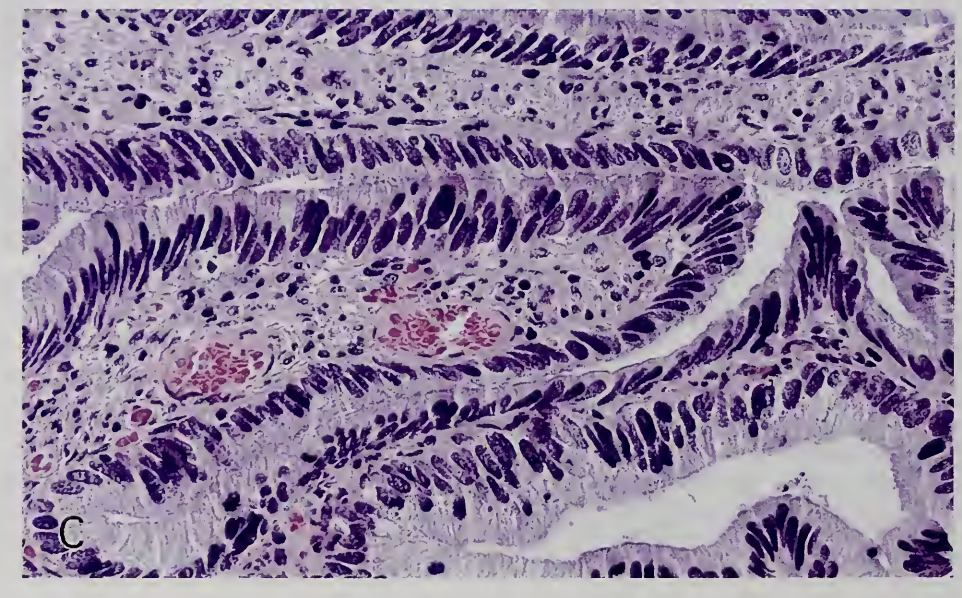


Figure 5-88

ATYPICAL GLANDULAR CELLS, FAVORING ADENOCARCINOMA IN SITU

A: Atypical endocervical cells in a cytologic smear have enlarged, crowded nuclei with coarsely granular chromatin and prominent nucleoli.

B: In a liquid-based cytologic preparation the atypical cells have enlarged, crowded nuclei with granular chromatin and prominent nucleoli.

C: The biopsy specimen has partially distorted epithelium but demonstrates sufficient nuclear atypia and mitotic activity to confirm a diagnosis of AIS.

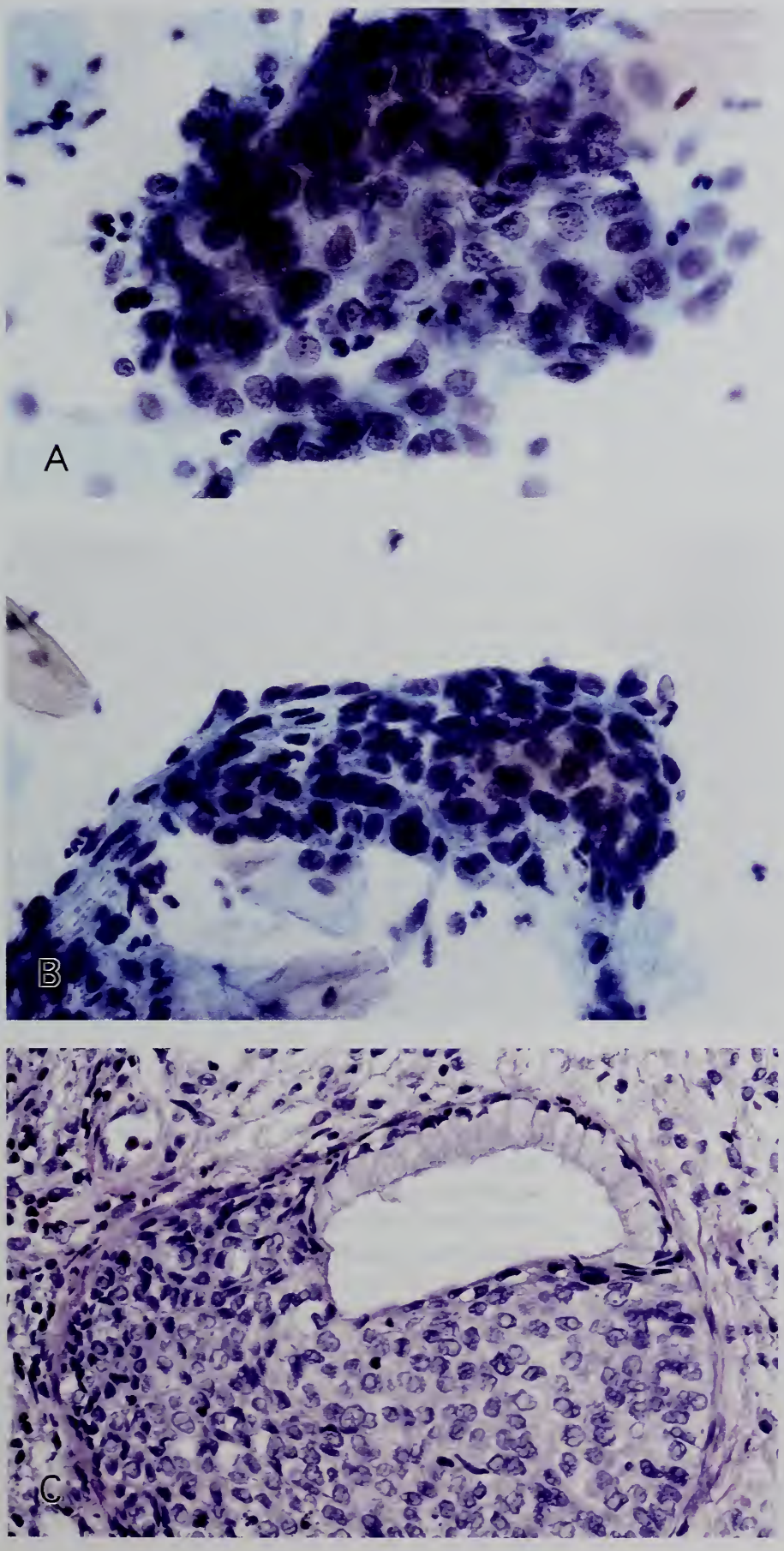


Figure 5-89

ATYPICAL ENDOCERVICAL GLANDULAR CELLS, FAVORING NEOPLASIA (AIS VERSUS HSIL BASED ON ENTIRE SPECIMEN)

A: Hypercellular aggregate in a cytologic smear contains cells with delicate cytoplasm and enlarged atypical nuclei, suggesting an endocervical glandular neoplastic process but other cells and the follow-up tissue specimen indicate HSIL without AIS.

B: A fragment of atypical epithelium in a cytologic smear initially interpreted as atypical glandular cells based on features illustrated in figure A demonstrates flattened cells parallel to the tissue edge rather than peripheral palisaded cells (feathering), indicating squamous rather than glandular differentiation.

C: A biopsy specimen confirms the presence of a squamous lesion (HSIL) involving a gland rather than a true glandular lesion.

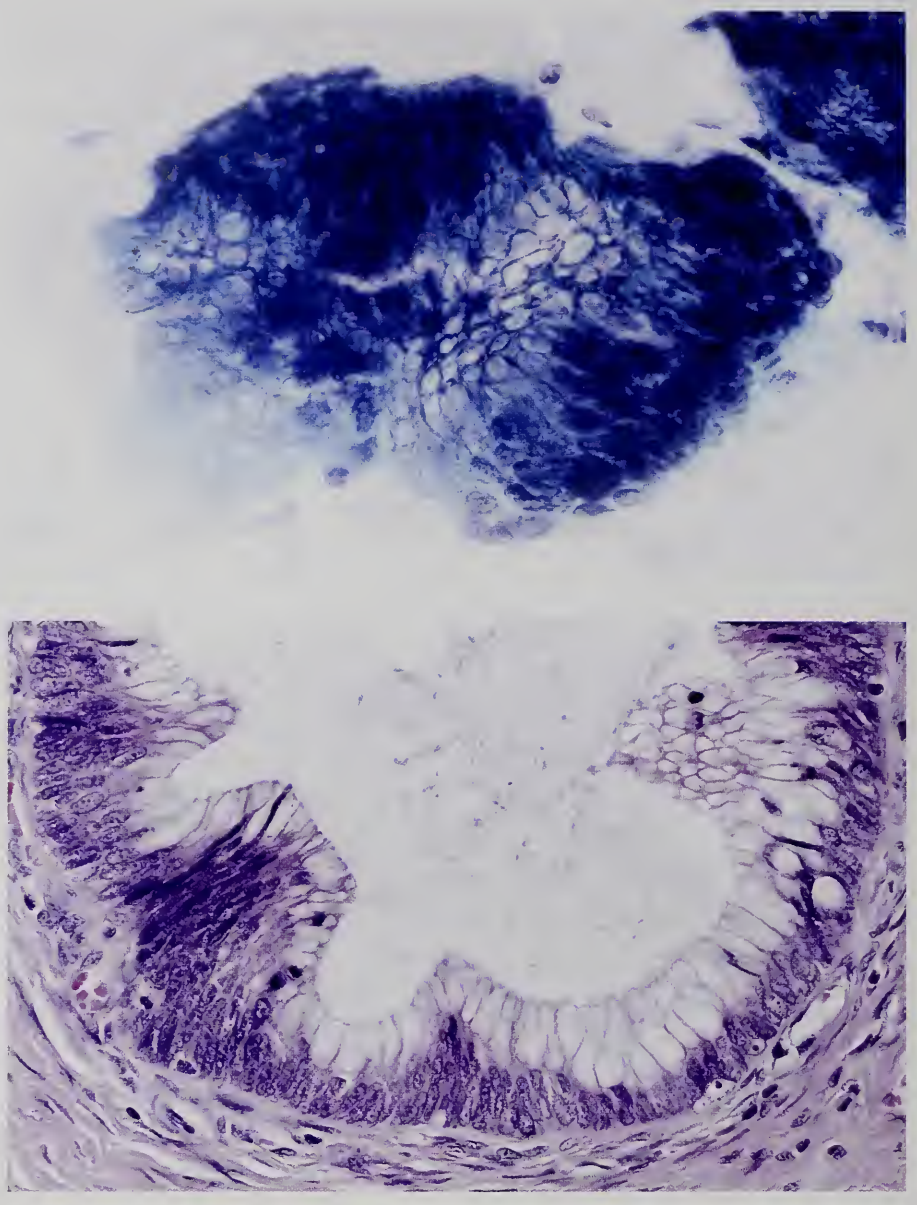


Figure 5-90

ADENOCARCINOMA IN SITU, INTESTINAL TYPE

Top: A cytologic smear contains atypical columnar mucinous epithelium with goblet cells.

Bottom: A biopsy specimen corresponding to the cytologic preparation shows atypical endocervical epithelium with intestinal type mucinous differentiation.

and follow-up cytology for SILs. Given the high prevalence of HPV in AIS, HPV testing as follow-up for AIS should be considered.

Adenocarcinoma

In the past, approximately 95 percent of all invasive cervical carcinomas were classified as squamous carcinomas and only 5 percent as *adenocarcinomas* (274). The relative frequency of adenocarcinoma has been increasing due to a decrease in the frequency of invasive squamous cell carcinoma, but there has also been an absolute increase in the incidence of adenocarcinoma (238,398,420). In a population-based study using the SEER data base, it was found that in the last quarter of a century, the age-adjusted incidence rates for all invasive cervical cancers (squamous and glandular) decreased by 37 percent but the age-adjusted incidence rates for adenocarcinoma increased by nearly 30 percent. The increase was 104 percent relative to all cervical cancers (379). Since the early 1970s, most studies have found that squamous cell carcinomas account for 75 to 80 percent of all cervical carcinomas while 20 to 25 percent include various types of adenocarcinomas, adenosquamous carcinomas, and undifferentiated carcinomas (167).

Patients with adenocarcinoma share many of the epidemiologic risk factors of invasive squamous carcinoma. These include an interval of more than 5 years since the last Pap smear, number of lifetime sexual partners, young age

at first sexual intercourse, a history of genital infections, obesity, and cigarette smoking. Most importantly, nearly 60 percent of cervical adenocarcinomas are associated with SIL or invasive squamous carcinoma (249,348), and about 90 percent of adenocarcinomas contain HPV nucleic acid sequences (15,320,427). There is a preferential distribution of HPV 18 in adenocarcinomas compared to squamous carcinomas but the reason for this is not clear. There continues to be controversy over whether long-term use of oral contraceptives is a risk factor. Most recent studies comparing invasive adenocarcinomas with invasive squamous cell carcinomas have found no significant difference after controlling for HPV and sexual factors (232).

Women with Peutz-Jeghers syndrome appear to have a genetic predisposition to invasive cervical adenocarcinoma, specifically, minimal deviation adenocarcinoma. These women also tend to have mucinous tumors of the ovary (199,440). The ovarian tumors that accompany adenocarcinoma of the cervix are usually independent primary neoplasms.

The mean age of patients with adenocarcinoma of the cervix is between 47 and 53 years. Most reports suggest that women with adenocarcinoma are a few years older than those with squamous cell carcinoma. The symptoms of patients with adenocarcinoma of the cervix are similar to those with squamous cell carcinoma: about 75 percent of patients present with vaginal bleeding and some women present with a discharge. Adenocarcinomas of different cell types are associated with similar symptoms. It has been stated that only a minority of adenocarcinomas are detected by cytology, but in most large series the majority of patients have cytologic abnormalities (19). At the time of discovery of the tumor, about 85 percent of women have disease limited to the cervix (stage I) or extending into the parametrium or upper vagina (stage II).

Microinvasive Adenocarcinoma (Early Invasive Adenocarcinoma)

There is no consensus regarding the validity of the concept or the criteria for *microinvasive adenocarcinoma*. Certainly, clear-cut evidence of minimal invasion can be seen in some cases, but recognizing early invasion is extremely difficult. Moreover, the maximum depth of invasion that is associated with a negligible risk of local lymph node metastasis has not been established.

Two unequivocal features of early invasion are: 1) individual cells or small nests of malignant-appearing cells adjacent to AIS, and 2) malignant-appearing glands surrounded by a desmoplastic reactive stroma (445). Unfortunately, more often than not, early invasive adenocarcinomas do not display these features, in which case other, more subtle, less specific features must be used to distinguish this lesion from AIS. These include: 1) a haphazard pattern of glands that do not retain the usual lobular architecture of the glands in AIS; 2) complex, branching glands or small glands displaying a confluent pattern; 3) a cribriform pattern within what appears to be a single glandular structure; and 4) isolated small glands that are below the deep margin of normal glands in the specimen, particularly if these glands are intimately associated with large blood vessels (figs. 5-91–5-98).

There is also no agreement as to how the measurement of "invasion" should be made. Since it may be difficult or impossible to distinguish the glands of AIS from glands of superficially invasive adenocarcinoma and thereby determine precisely where invasion started (307), the recent World Health Organization (WHO) Classification (399a) recommends not measuring the depth of invasion but rather measuring the thickness of the tumor from the surface of the epithelium to the deepest point of invasion. The lateral extent of the tumor should be measured. Although in the largest study of these tumors in which invasion was limited to 5 mm from the surface basement membrane, there was no evidence of parametrial or nodal disease (306), other studies have reported metastasis from tumors invading from 2 to 5 mm (37,104).

There appears to be a biologic continuum for adenocarcinoma of the cervix, with an increasing risk of metastasis that correlates with depth of invasion (445). The limited data, however, do not permit assigning a particular depth of invasion for which there is a negligible risk of metastasis. Accordingly, we do not recommend using the term "microinvasive adenocarcinoma." Instead, we measure either the depth of invasion when there are only small foci of invasion immediately adjacent to AIS or the thickness

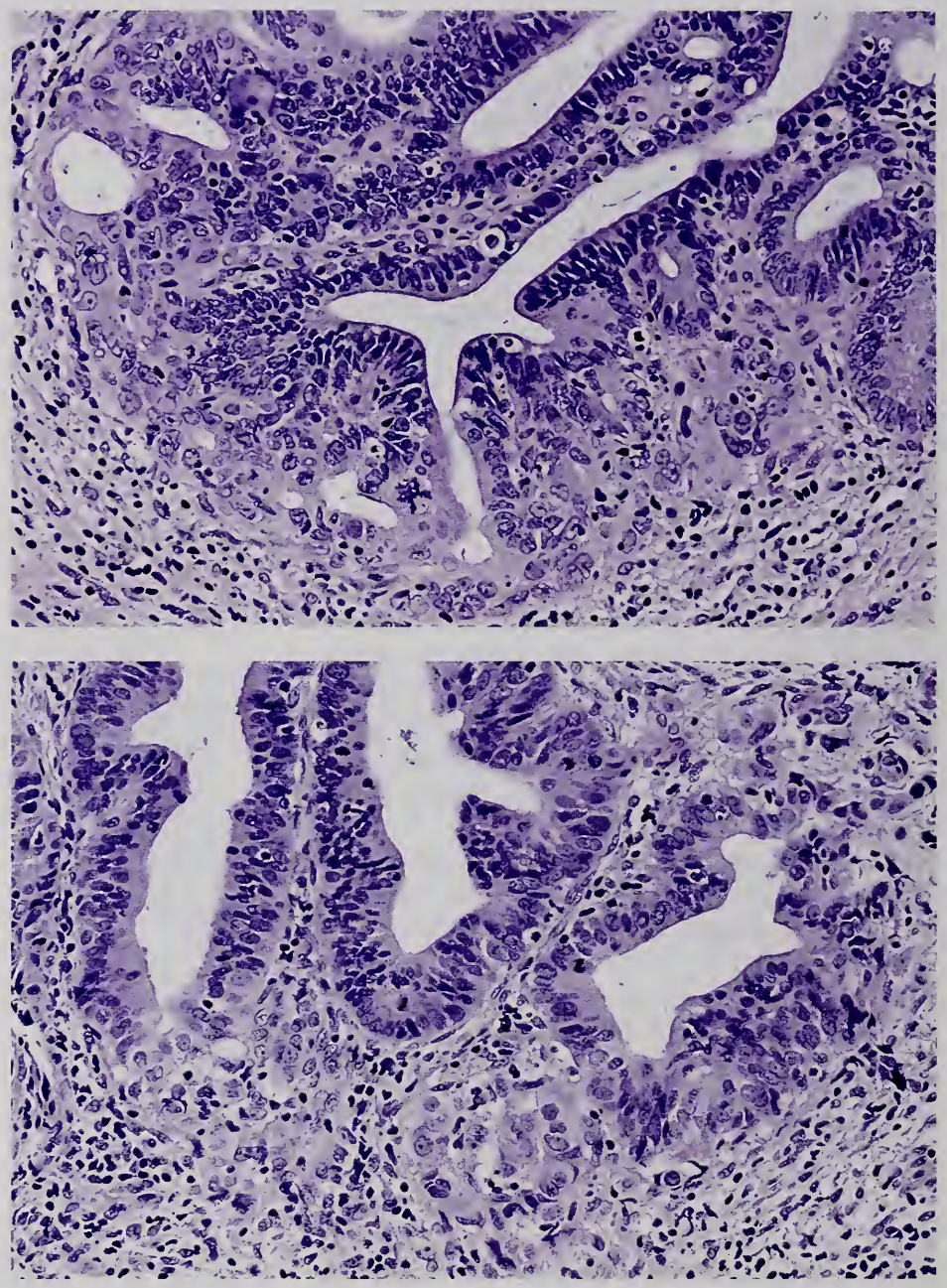


Figure 5-91

ADENOCARCINOMA IN SITU WITH EARLIEST RECOGNIZABLE FORM OF INVASIVE ENDOCERVICAL ADENOCARCINOMA

Top: The lesion is characterized by budding, cribriform, atypical glandular epithelium, with cells exhibiting increased amounts of eosinophilic cytoplasm along the base of the AIS; an atypical mitotic figure is present as well.

Bottom: The lesion is characterized by small clusters of markedly atypical glandular cells with increased amounts of eosinophilic cytoplasm situated within inflamed reactive stroma adjacent to the AIS.

of the entire lesion when the precise origin of invasion cannot be identified. The diagnosis of invasion is based on the overall growth pattern and the entire tumor is interpreted to be invasive. The lateral extent of the tumor should also be measured.

Invasive Adenocarcinoma

General Features. Cervical adenocarcinoma displays a wide variety of morphologic phenotypes but most (probably over three quarters) are remarkably similar. Traditionally, these tumors were classified as mucinous adenocarcinomas but most of these do not have a conspicuous mucinous appearance on hematoxylin and eosin (H&E) stains (433). They have a typical appearance, however, characterized by epithelium having a hybrid of mucinous and endometrioid differentiation in which columnar cells have enlarged, elongated hyperchromatic nuclei and some apical eosinophilic cytoplasm. There is abundant mitotic activity, with mitotic figures typically situated in the apical cytoplasm, and apoptotic bodies frequently present. This

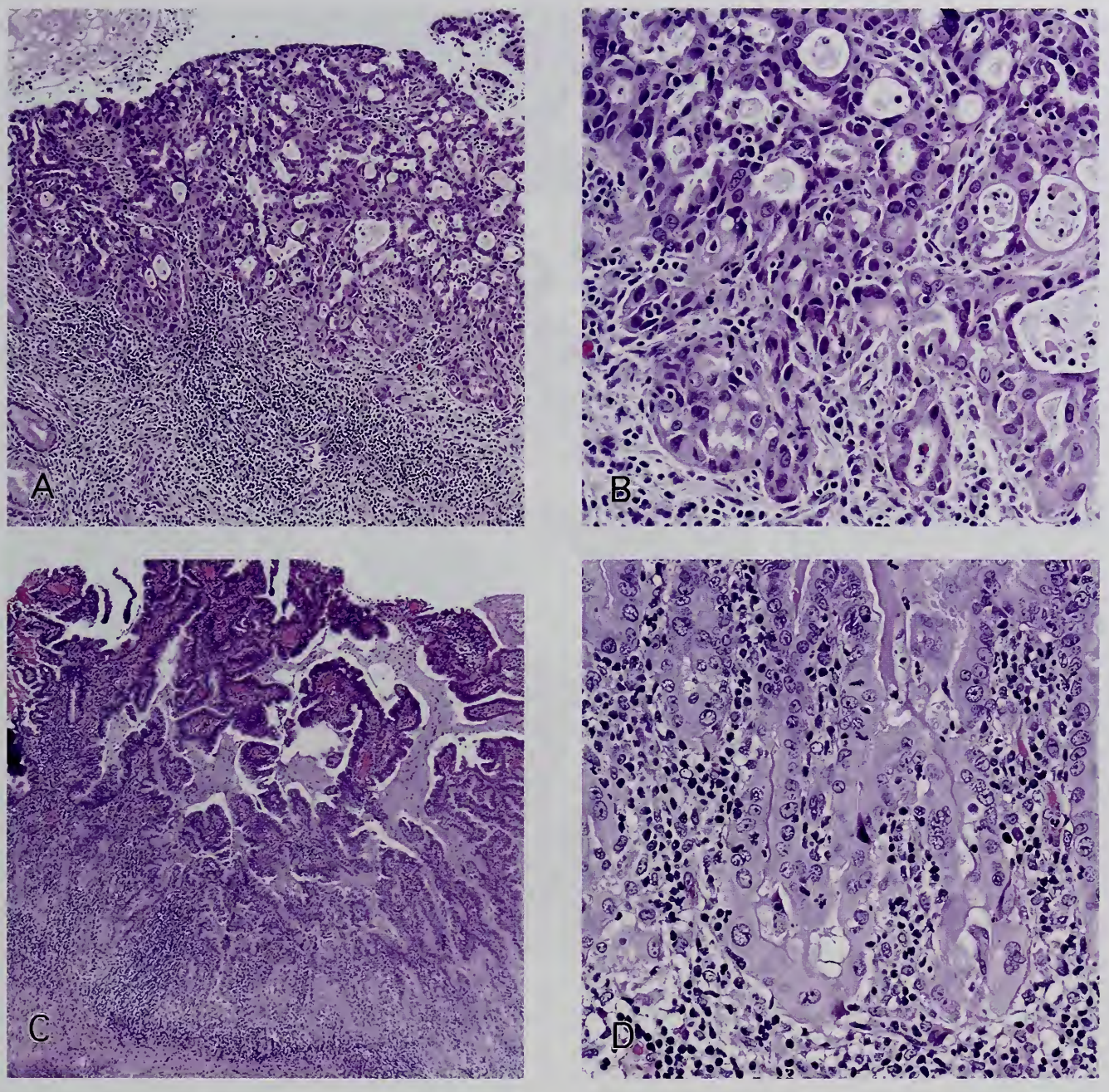


Figure 5-92

EARLY INVASIVE ENDOCERVICAL ADENOCARCINOMA

A: A cribriform glandular proliferation, measuring only 2 mm in horizontal extent and 1 mm in thickness, invades the cervical stroma.

B: At higher magnification, cribriform glands are present within inflamed, reactive superficial cervical stroma.

C: A confluent glandular and papillary proliferation, measuring only several millimeters in horizontal extent and thickness, involves the endocervical mucosa and superficial cervical stroma.

D: At higher magnification, markedly atypical glands with abundant eosinophilic cytoplasm extend into the inflamed cervical stroma. This is the invasive front of the adenocarcinoma.

appearance is similar to, yet distinctly different from, the typical endometrioid carcinoma of the endometrium. These tumors can be designated simply *endocervical adenocarcinomas of usual type* (434). True endometrioid type adenocarcinomas of the endocervix are uncommon, representing no more than 10 percent of cervical adenocarcinomas. The remainder of cervical

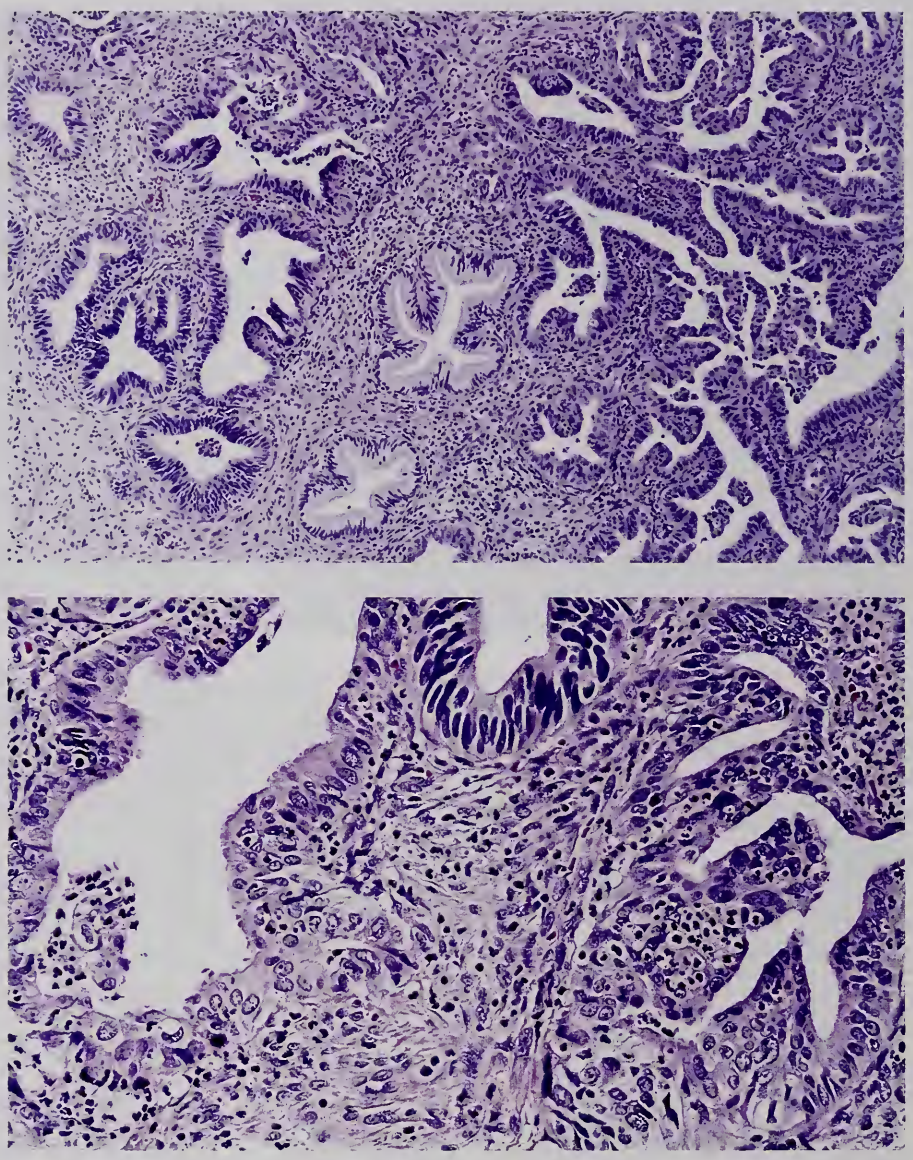


Figure 5-93

ADENOCARCINOMA IN SITU WITH INVASIVE ADENOCARCINOMA

Top: Glands of invasive adenocarcinoma are irregularly branching and labyrinthine whereas individual glands of AIS are discrete and more basophilic.

Bottom: Markedly atypical, irregular glands of invasive adenocarcinoma are composed of cells with abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli. A single partial gland of AIS has distinctive elongated hyperchromatic nuclei.

adenocarcinomas comprises a diverse group that includes intestinal type mucinous adenocarcinoma, mucinous adenocarcinoma with signet ring cell differentiation, minimal deviation adenocarcinoma, villoglandular endometrioid adenocarcinoma, clear cell carcinoma, serous carcinoma, mesonephric adenocarcinoma, and a number of uncommon variants.

Gross Findings. About half of cervical adenocarcinomas are exophytic, polypoid, or papillary masses. The others are nodular, with diffuse enlargement or ulceration of the cervix. Approximately 15 percent of patients have no visible lesion because the carcinoma is within the endocervical canal or infiltrative and small. Even in the absence of visible signs or symptoms, the lesion may infiltrate deeply into the wall.

Microscopic Findings. Adenocarcinomas exhibit a variety of patterns and are composed of diverse cell types, which often appear in combination. Because intermixtures are common, the designation of type is based on the predominant component. Generally, it is not necessary to mention the presence of other components as this does not appear to affect the prognosis or alter treatment. An important exception is the presence of another component in what is predominantly a well-differentiated villoglandular carcinoma, because the excellent prognosis of villoglandular carcinoma is adversely affected by the presence of another component. Moreover, conservative treatment, which is appropriate for pure well-differentiated villoglandular carcinoma, is contraindicated if

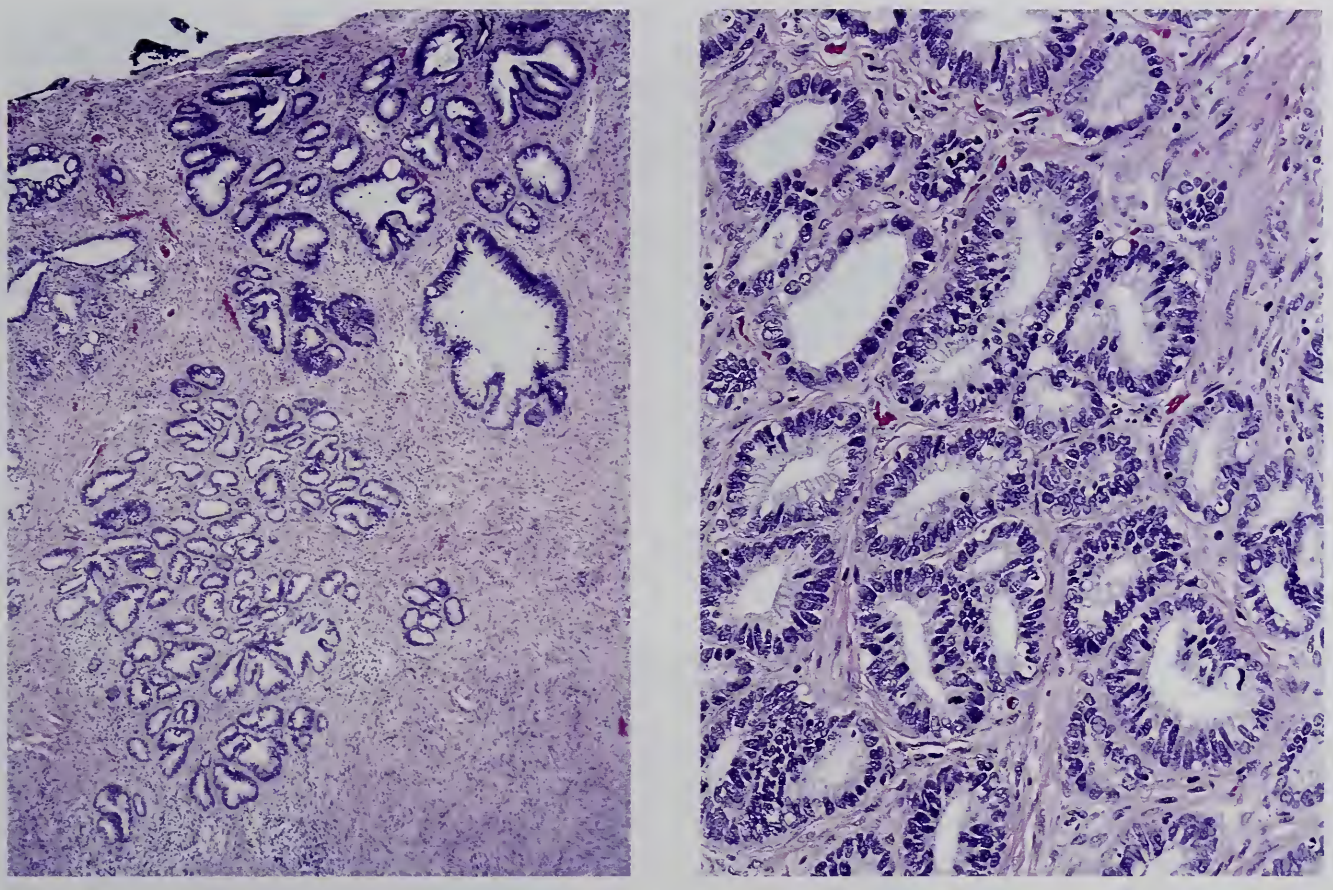


Figure 5-94

ADENOCARCINOMA IN SITU WITH PROBABLE INVASION

Left: An aggregate of small, tightly and haphazardly clustered glands below the AIS suggests possible invasion.
Right: Glands within the deeper aggregate of the lesion are smaller, tightly clustered, and some are fused together; these features are highly suggestive of invasion.

another histologic type is present. Although there are no data on the behavior of mixed tumors containing a serous component, based on experience with similar tumors in the uterine corpus, it is advisable to note this component in the pathology report.

The most common type of adenocarcinoma is endocervical adenocarcinoma, usual type, which accounts for approximately three quarters of all endocervical adenocarcinomas (figs. 5-99–5-101). It has been traditionally referred to as mucinous carcinoma, but as noted earlier, these neoplasms have little if any intracytoplasmic mucin evident on H&E slides or, for that matter, with mucin stains. Although it bears a superficial resemblance to endometrioid carcinoma, this usual type of endocervical adenocarcinoma has a distinctive appearance characterized by glands exhibiting a hybrid of mucinous and endometrioid differentiation, as noted above. The glands may be widely separated or arranged in a complex racemose pattern simulating the cleft-tunnel configuration of the normal endocervix. A cribriform architecture is very common and complex papillae may project into gland lumens. The cells contain amphophilic or eosinophilic cytoplasm and are typically stratified. There may be marked nuclear atypia with nuclear pleomorphism, coarse chromatin, and prominent nucleoli. The mitotic index is usually high and apoptotic bodies are almost always evident. HSIL or invasive squamous cell carcinoma may coexist with an invasive adenocarcinoma.

Microscopic Grading. Endocervical adenocarcinomas are graded on the basis of architectural features, similar to endometrial adenocarcinomas. They are graded as well differentiated if less

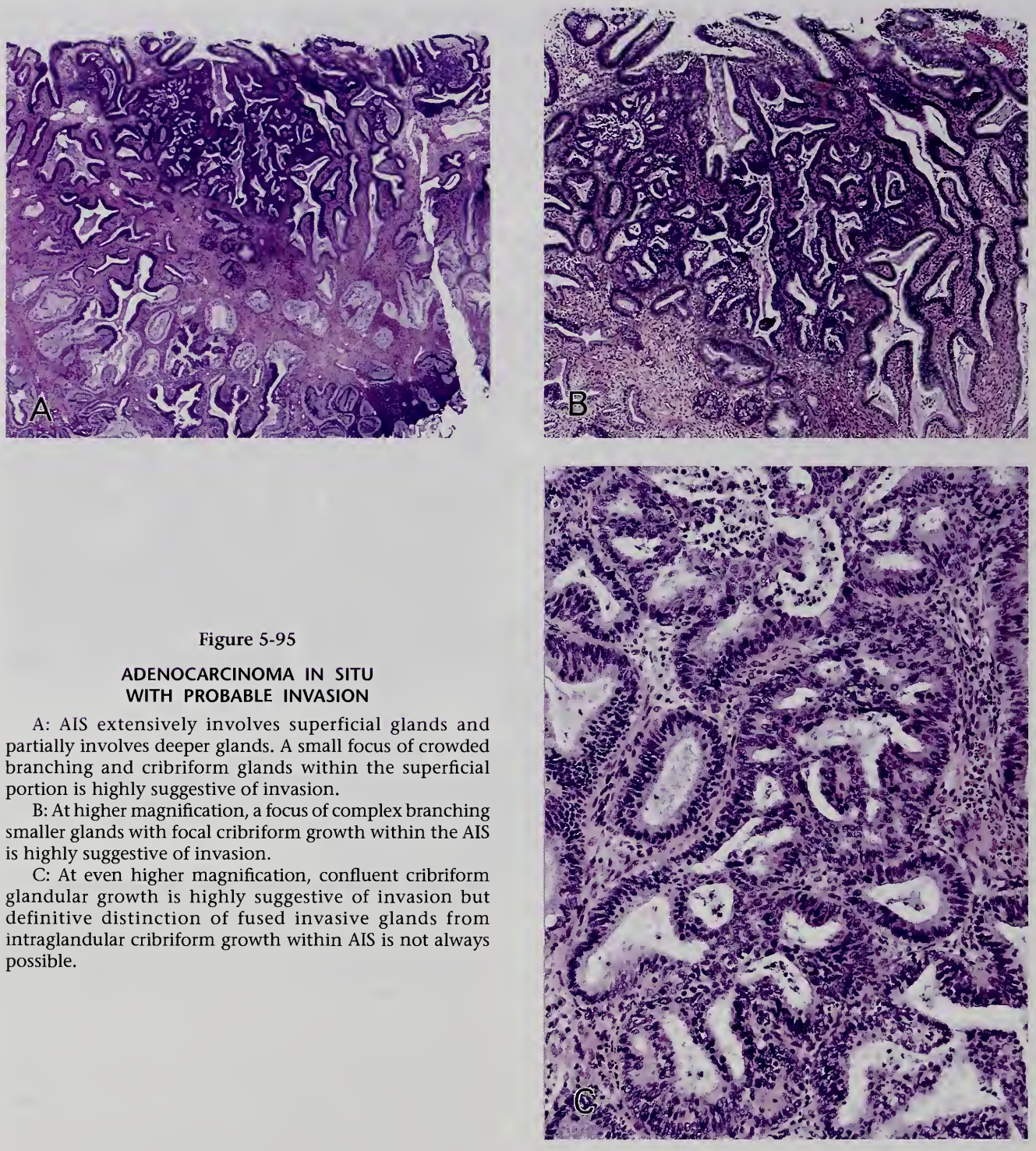


Figure 5-95

ADENOCARCINOMA IN SITU WITH PROBABLE INVASION

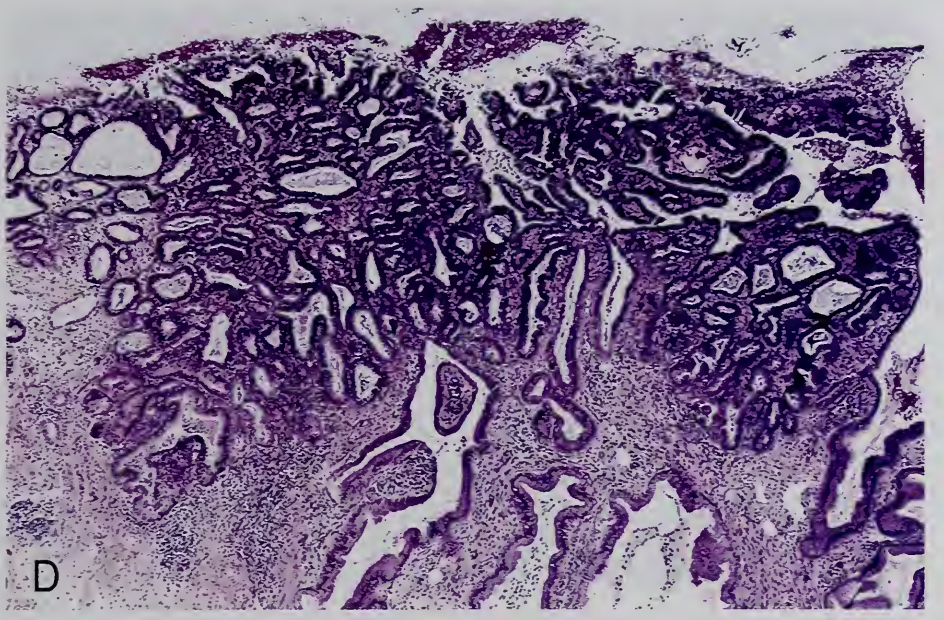
A: AIS extensively involves superficial glands and partially involves deeper glands. A small focus of crowded branching and cribriform glands within the superficial portion is highly suggestive of invasion.

B: At higher magnification, a focus of complex branching smaller glands with focal cribriform growth within the AIS is highly suggestive of invasion.

C: At even higher magnification, confluent cribriform glandular growth is highly suggestive of invasion but definitive distinction of fused invasive glands from intraglandular cribriform growth within AIS is not always possible.

than 10 percent of the tumor is solid, moderately differentiated if 11 to 50 percent is solid, and poorly differentiated if more than 50 percent of the tumor is solid. By these criteria, endocervical adenocarcinomas are well differentiated but their behavior does not always correspond as it would for well-differentiated carcinomas of the uterine corpus. Nuclear grading has little to support its use since in our experience it is not reproducible. Tumor size and depth of invasion are more important prognostic features.

The depth of invasion should be expressed as percent of involvement of the wall. When invasion is superficial, a measurement of the depth in millimeters can be provided. Measurement of the depth of invasion of adenocarcinoma,



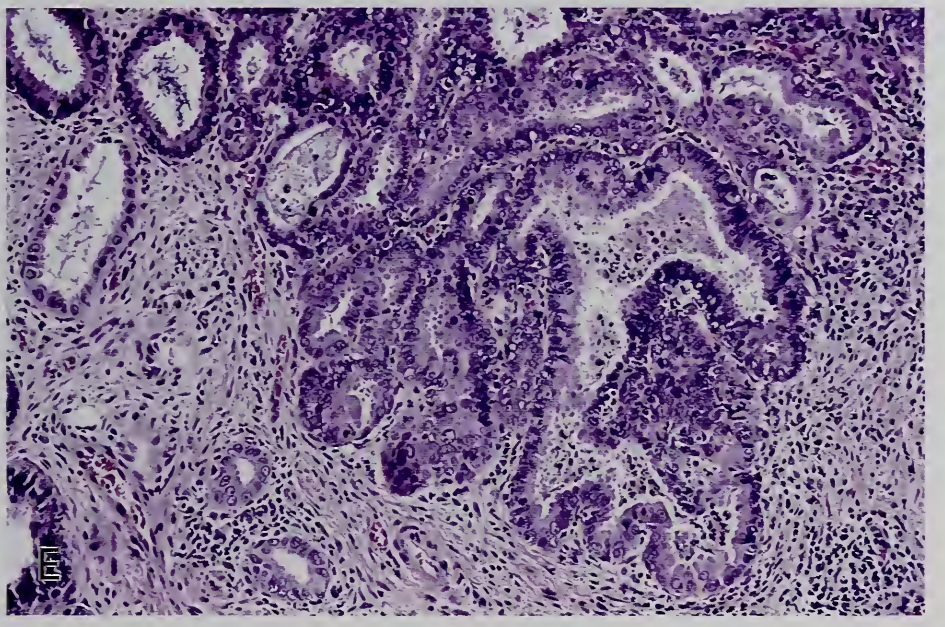


Figure 5-95 (Continued)

D: The lesion represents at least extensive AIS, but numerous crowded smaller glands and focal confluence of branching superficial glands are highly suggestive of invasion.

E: At higher magnification, two isolated small atypical glands, an aggregate of tightly clustered smaller glands, and one larger complex gland within inflamed reactive stroma are highly suggestive of invasion.

however, is more subjective than in cases of squamous cell carcinoma because of the difficulty in determining the point of origin. The presence or absence of vascular space invasion should also be determined.

Immunohistochemical and In Situ Hybridization Findings. Immunohistochemistry can assist in the distinction of endocervical from endometrial adenocarcinoma and in distinguishing AIS from benign glandular proliferations. It is of no value, however, in distinguishing AIS from early invasive endocervical adenocarcinoma. Some studies have found that CEA and vimentin are useful for differentiating endocervical and endometrial adenocarcinomas (59,90,262). Although many endocervical adenocarcinomas are CEA positive and many adenocarcinomas of the uterine corpus are CEA negative, those endometrial tumors having mucinous differentiation may be strongly positive, thus limiting the value of this marker (79,91). CEA has some utility in distinguishing benign lesions of the cervix from adenocarcinoma because normal endocervical mucosa and most benign lesions of the cervix are CEA negative, but microglandular hyperplasia is an

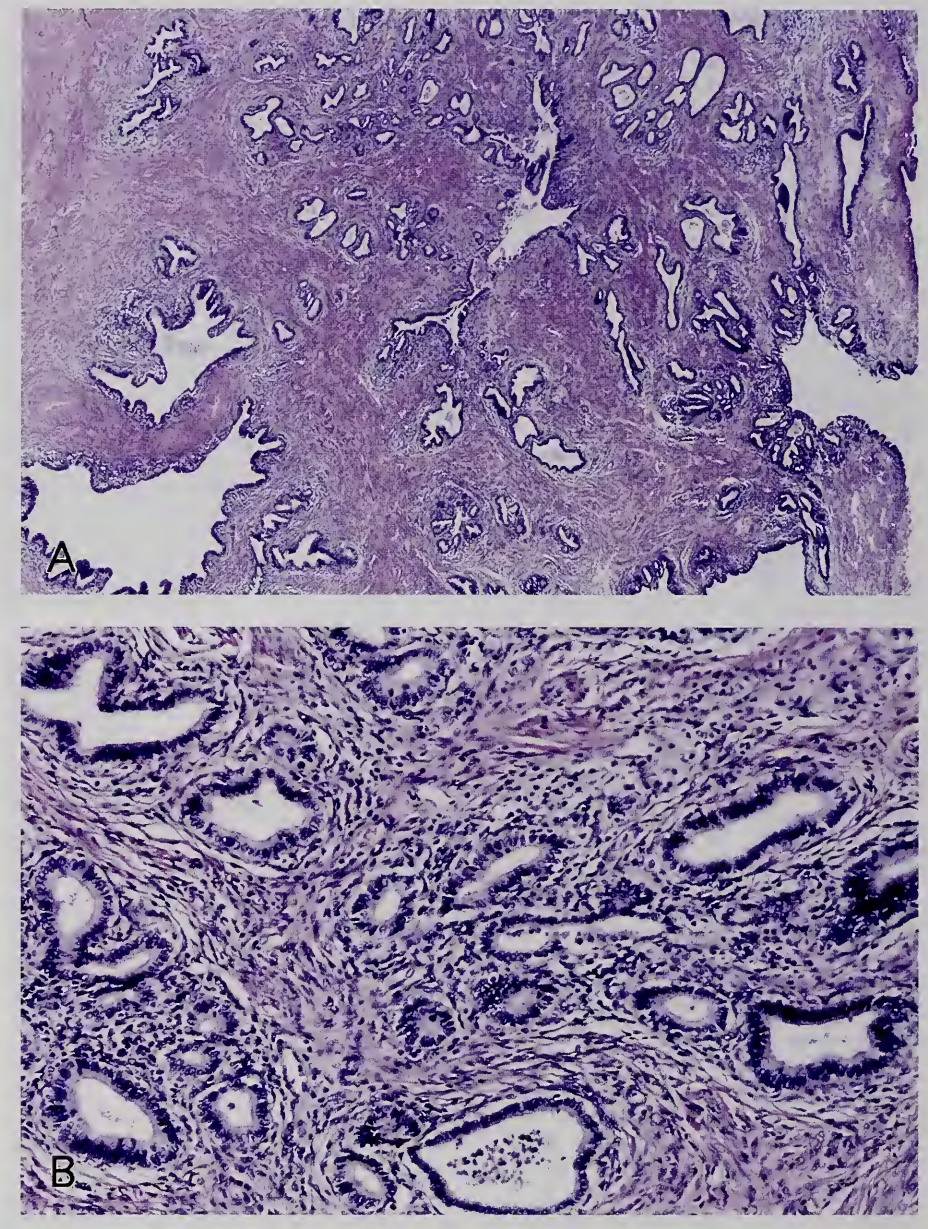


Figure 5-96

EXTENSIVE ADENOCARCINOMA IN SITU WITH INVASIVE ADENOCARCINOMA

A: Atypical glandular proliferation appears to conform to the pattern of normal endocervical glands more superficially but extends deep into cervical stroma. The atypical glands are highly variable in size and shape and exhibit a haphazard growth pattern.

B: At higher magnification, glands of variable size and shape are surrounded by inflamed fibrous stroma.

exception because it is uniformly CEA positive. In an individual case, CEA is not specific in differentiating endometrial carcinoma from endocervical carcinoma, or in differentiating a benign lesion from an adenocarcinoma.

Immunostaining for hormone receptors (both estrogen [ER] and progesterone [PR] receptors) and p16 can be useful in distinguishing endocervical from endometrial adenocarcinomas (20,122,128,177,256,260,289,383,451). Generally, both ER and PR are expressed in well to moderately differentiated endometrioid carcinomas of the endometrium and p16 expression ranges from negative to patchy or multifocal with weak to moderate intensity (figs. 5-100, 5-102, 5-107, 5-109, 5-111). In contrast, high-risk HPV-related endocervical adenocarcinomas usually show loss of hormone receptor expression and exhibit diffuse, strong expression of p16 Occasional HPV-related endocervical adenocarcinomas retain hormone receptor expression (more often ER than PR) and serous carcinoma of the endometrium is typically diffusely and strongly positive for p16, so these assays are not entirely specific for tumors of one origin rather than the other. Additional features (clinical, morphologic, HPV detection) are required for determining the site of origin in these cases.

In situ hybridization for high-risk HPV types is the most specific test available for

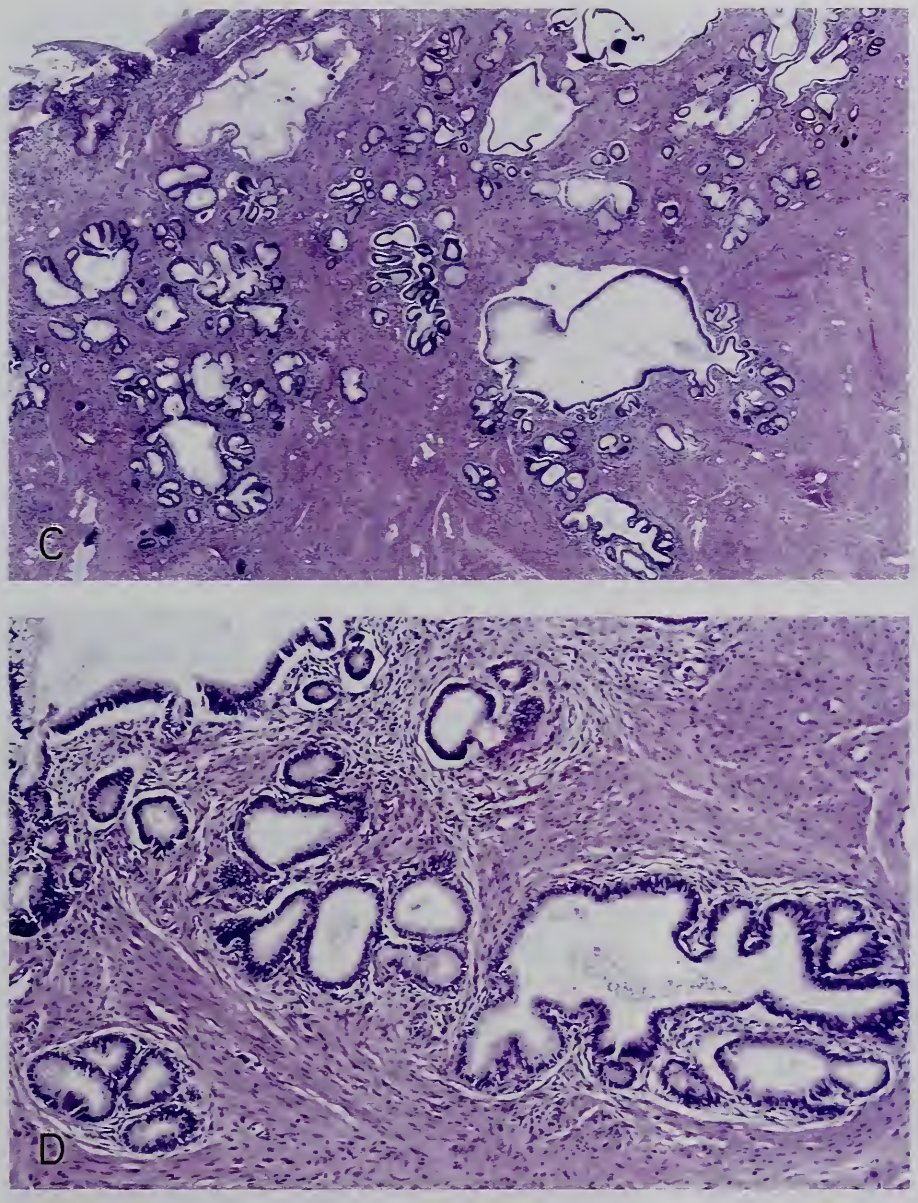


Figure 5-96 (Continued)

C: The glandular proliferation appears to conform to the pattern of normal endocervical glands but extends deep into the cervical stroma. Glands are irregularly shaped with marked variation in size and exhibit a haphazard growth pattern.

D: Small glands suggest AIS but represent a deep infiltrative extension of the haphazard proliferation seen in C.

distinguishing endocervical from endometrial adenocarcinoma since at least 90 percent of cervical adenocarcinomas contain high-risk HPV types (15,320,427) whereas endometrial carcinomas are considered etiologically unrelated to HPV infection. A positive in situ hybridization signal confirms that the tumor is a cervical neoplasm but lack of detectable HPV by this test does not exclude it, as we have encountered some tumors for which HPV was detected by PCR but not by in situ hybridization even when probes for the specific HPV type identified were used.

Differential Diagnosis. The major considerations in the differential diagnosis of adenocarcinoma of the cervix include both benign lesions such as microglandular hyperplasia and mesonephric hyperplasia, and malignant lesions such as AIS, extension of endometrial adenocarcinoma into the cervix, and adenocarcinoma metastatic to the cervix.

Microglandular hyperplasia occurs mainly in young women who are usually pregnant or are taking oral contraceptives, although it may occur in older women without a history of hormone intake. It tends to be polypoid and does not extend below the level of the normal endocervical glands. Microglandular hyperplasia is composed of small, relatively uniform glands that characteristically contain polymorphonuclear leukocytes. The glands typically undergo squamous

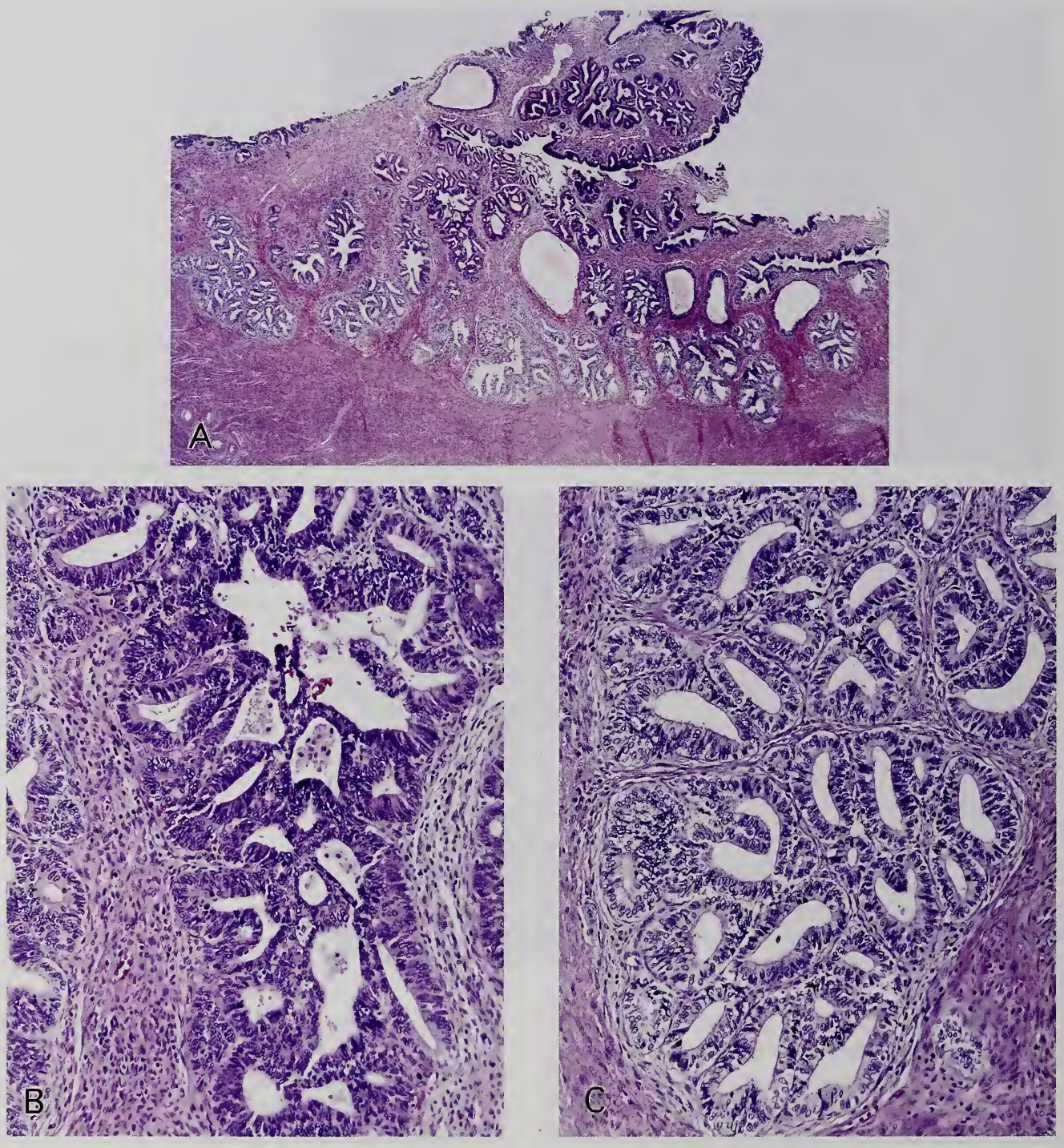


Figure 5-97

EXTENSIVE ADENOCARCINOMA IN SITU WITH SUPERFICIALLY INVASIVE ENDOCERVICAL ADENOCARCINOMA

A: The AIS has extensive horizontal spread and is focally polypoid. Tightly clustered small glands with focal cribriform growth along the basal aspect of the lesion are highly concerning for superficial stromal invasion; a concurrent morphologically identical ovarian tumor containing the same HPV type as the cervical lesion, consistent with a metastasis, supported interpretation as a subtle pattern of superficial invasion.

B: At higher magnification, an area of crowded glands exhibiting confluence within the superficial cervical stroma is highly suggestive of invasion. Intraglandular cribriform growth can occur in AIS and is not considered diagnostic of invasion; in this example, the complex profile of the proliferation indicates fusion of separate glands that have invaded stroma rather than an intraglandular (in situ) process.

C: Tightly clustered aggregates of small glands with focal gland fusion and reactive stroma are highly suggestive of invasion.

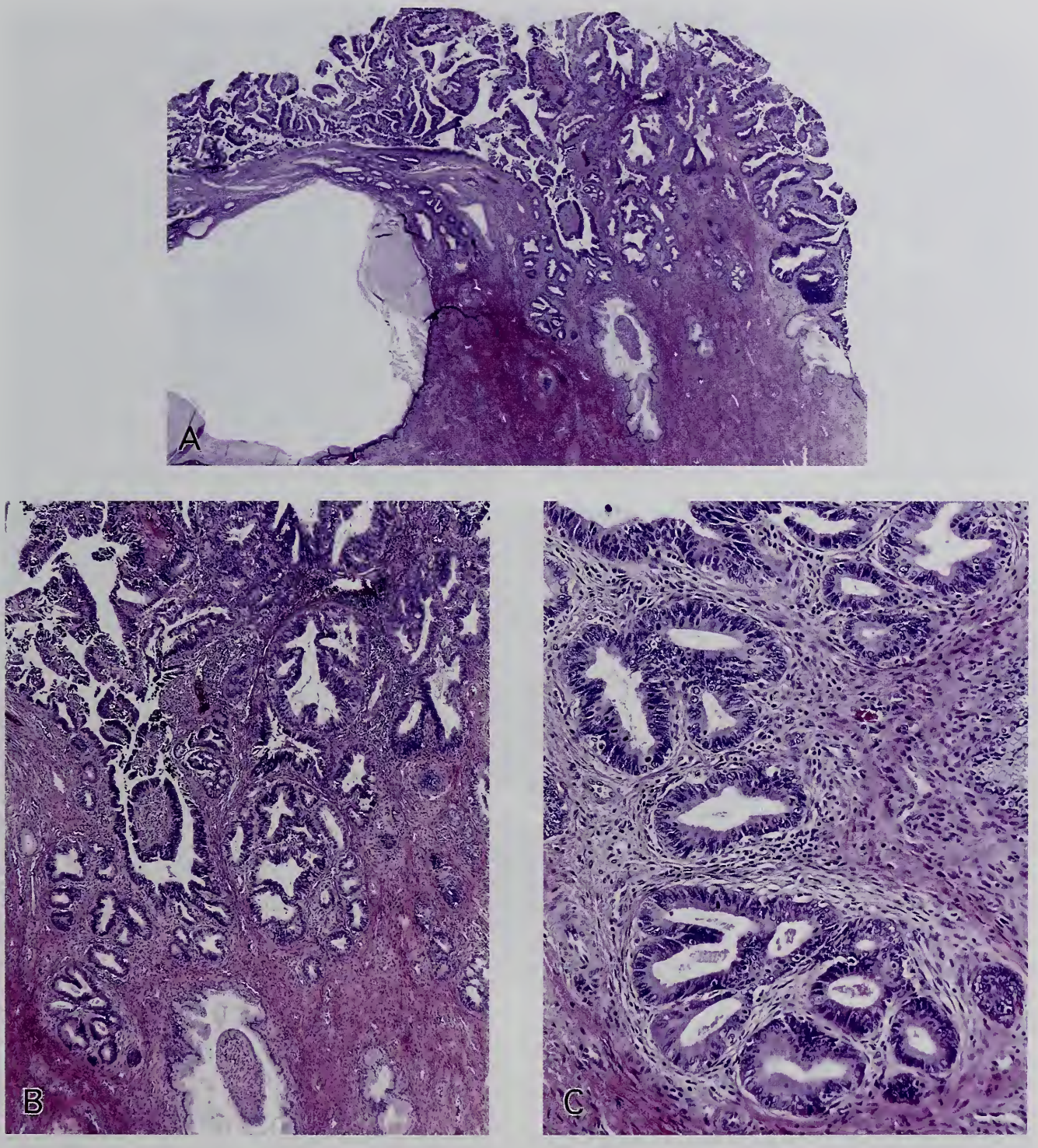


Figure 5-98

EXTENSIVE ADENOCARCINOMA IN SITU WITH SUPERFICIALLY INVASIVE ENDOCERVICAL ADENOCARCINOMA

A: The AIS has extensive horizontal spread and exhibits surface papillary villoglandular growth, a pattern highly suggestive of invasion. Small glands focally extend deep into superficial cervical stroma but not deeper than normal glands (a subsequent morphologically identical ovarian tumor containing the same HPV type as the cervical lesion, consistent with a metastasis, supports interpretation of the lesion as having a subtle pattern of superficial invasion).

B: Higher magnification shows that small glands within reactive superficial cervical stroma are situated between larger branching glands which exhibit villoglandular growth at the surface. Both patterns are highly suggestive of invasion.

C: Small glands in the deepest portion of the lesion are focally fused and surrounded by reactive stroma, highly suggestive of invasion.

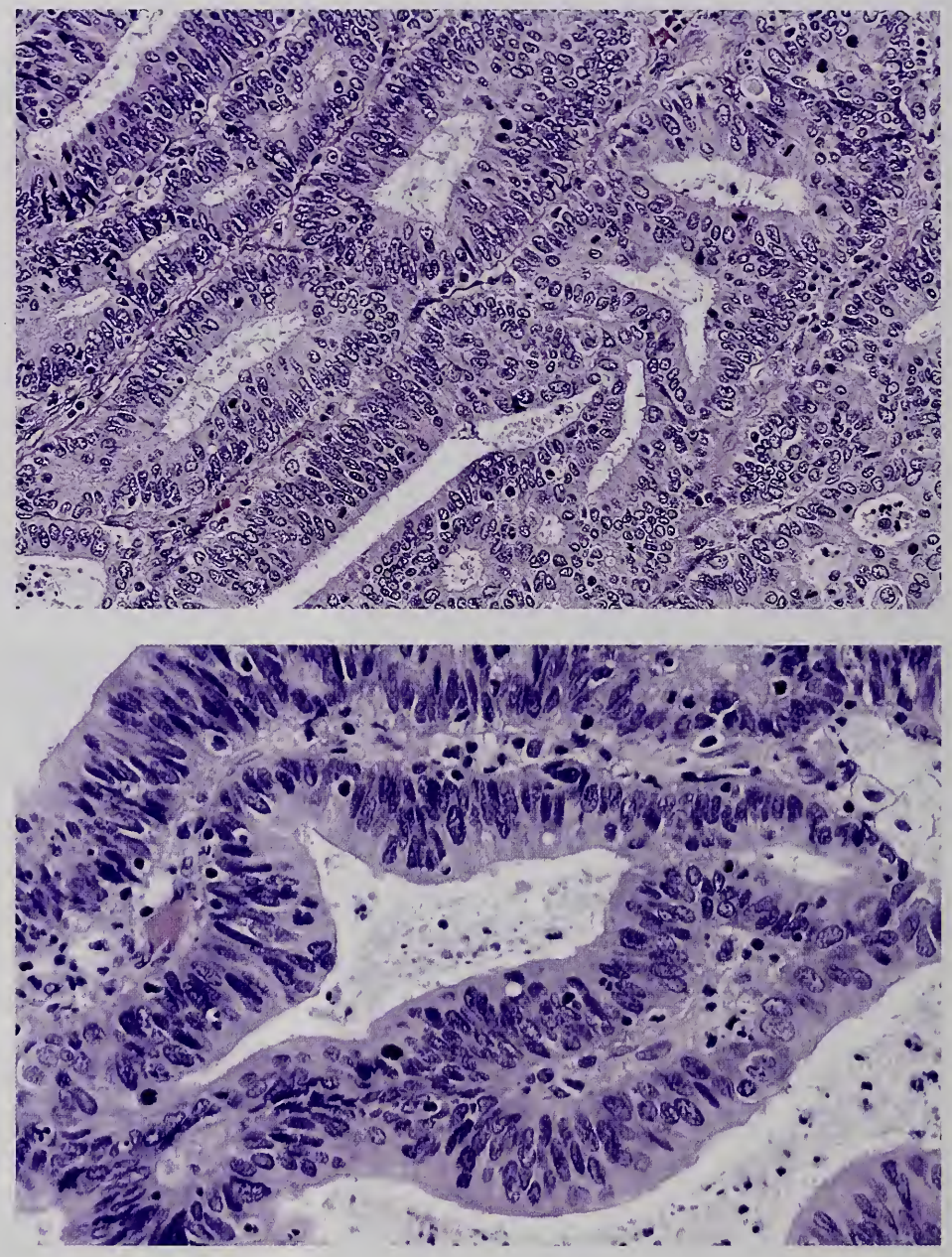


Figure 5-99

ENDOCERVICAL ADENOCARCINOMA, USUAL TYPE

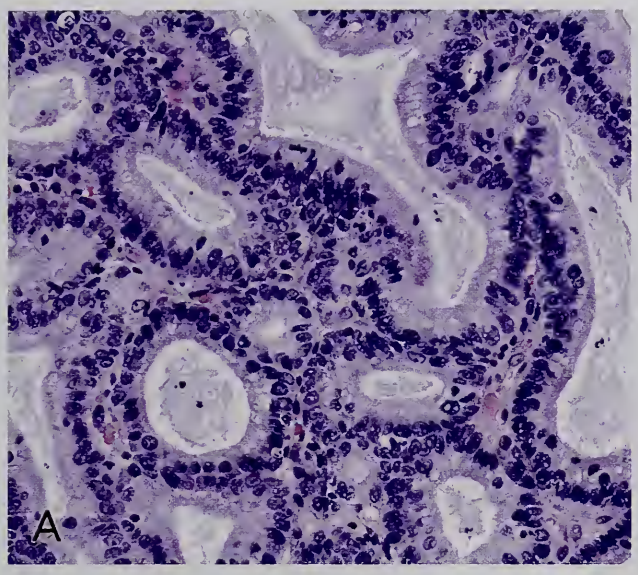
Top: Tumors with this appearance are often classified as "endometrioid" type due to the elongated nuclei and diminished mucinous cytoplasm.

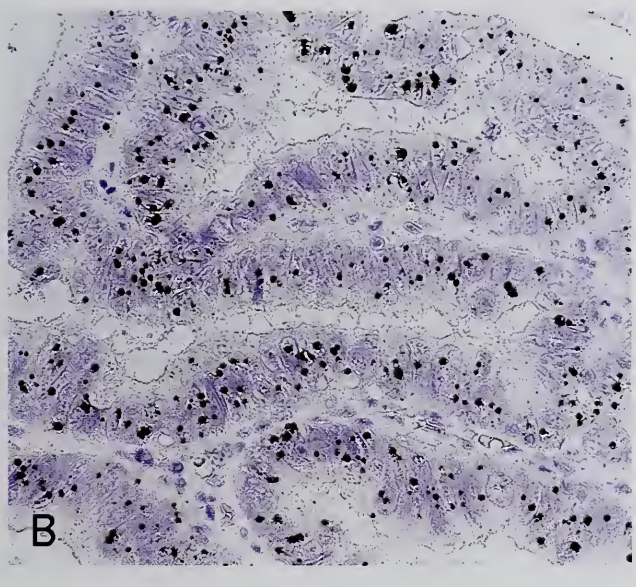
Bottom: The combination of elongated columnar nuclei and retained apical mucinous cytoplasm, indicating a hybrid of endometrioid and mucinous differentiation, characterizes the "usual type" adenocarcinoma. Numerous mitotic figures and apoptotic bodies also typify this high-risk HPV-related tumor.

metaplasia and mitotic activity is very low. Hyperplastic mesonephric remnants generally occur in clusters and are frequently associated with the mesonephric duct. Typically, the lesion is located deep in the wall of the cervix although it is not unusual for some of the tubules to extend to the surface. The tubules contain prominent eosinophilic material within their lumens, and usually have a well-demarcated peripheral basement membrane. Mitotic activity, cellular stratification, and nuclear atypia are minimal.

AIS differs from invasive adenocarcinoma in that the glands of AIS do not extend below the deep margin of normal endocervical glands and are not associated with a desmoplastic reactive stroma. In addition, the glands in AIS retain the usual lobular endocervical architecture and lack a complex, branching, confluent or extensive cribriform pattern.

Metastatic carcinoma to the cervix can usually be distinguished from primary endocervical adenocarcinoma by conventional clinicopathologic features. Nearly 90 percent of metastatic carcinomas to the cervix have evidence of widespread disease. There is usually extensive lymphatic permeation and the tumor is concentrated in the outer wall and soft tissues with minimal or absent surface involvement.





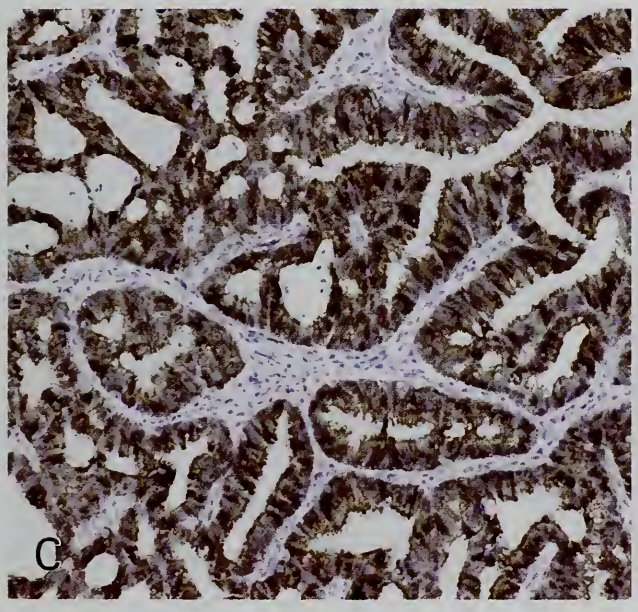


Figure 5-100

ENDOCERVICAL ADENOCARCINOMA, USUAL TYPE

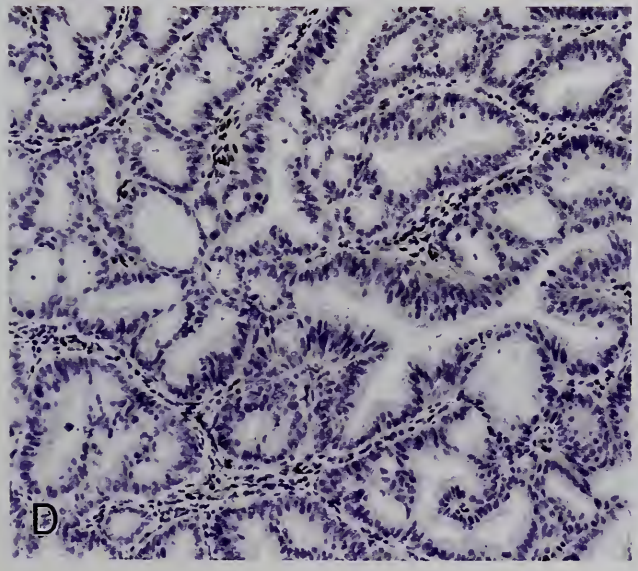
A: This tumor exhibits more mucinous cytoplasm than the example illustrated in figure 5-99, and may be classified as "mucinous" type by some.

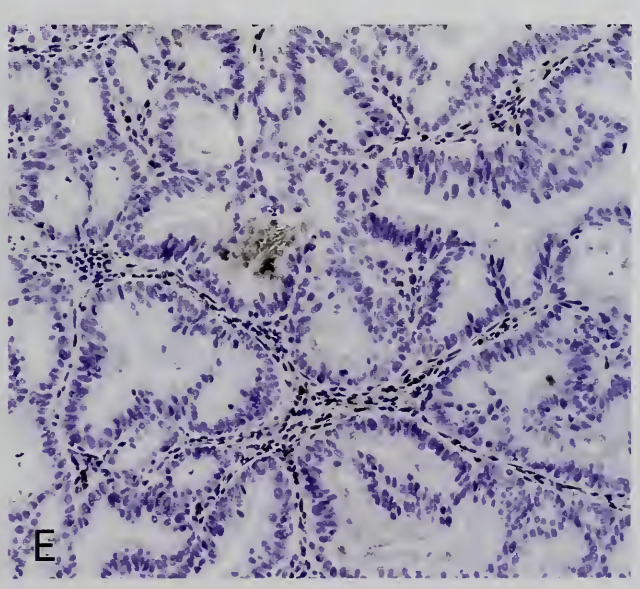
B: In situ hybridization for HPV 16 demonstrates the punctate nuclear signals indicative of a positive result. This pattern is thought to reflect integrated HPV. Most endocervical adenocarcinomas are HPV related and have usual type differentiation.

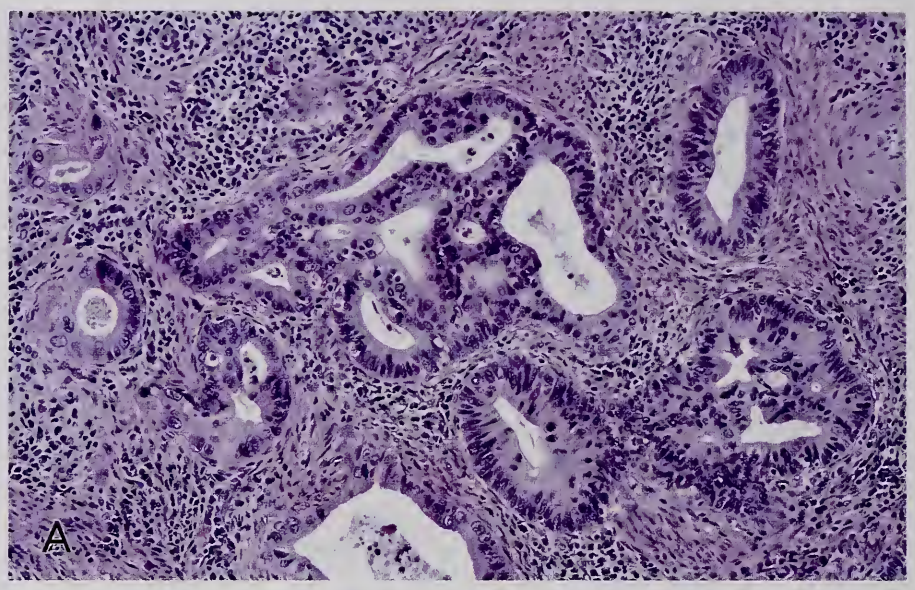
C: Diffuse strong expression of p16 by immunohistochemistry correlates with the presence of high-risk HPV.

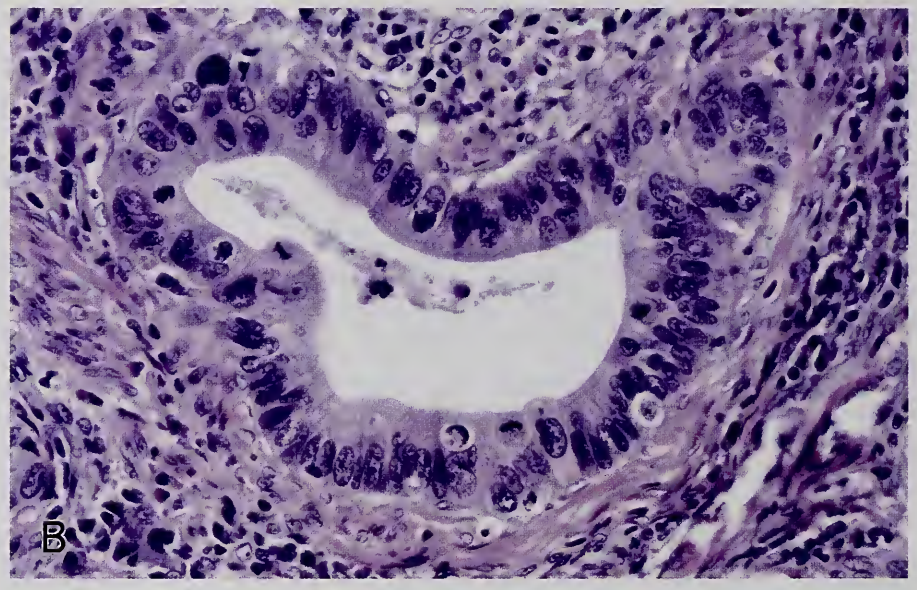
D: The tumor lacks expression of estrogen receptor (normal stroma serves as internal positive control).

E: Progesterone receptor expression is also lacking (normal stroma serves as internal positive control).









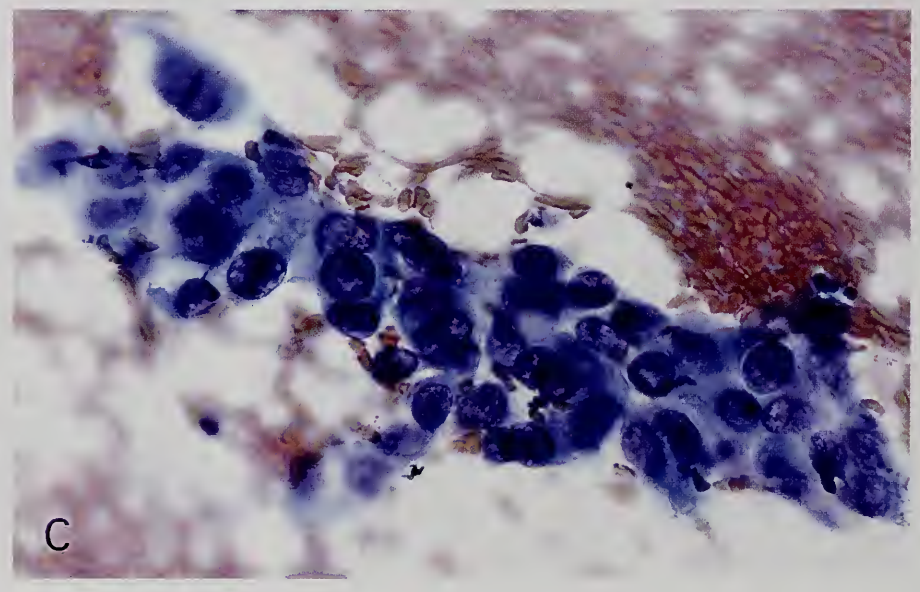


Figure 5-101

ENDOCERVICAL ADENOCARCINOMA

A: Invasion is characterized by variably sized glands within an inflamed desmoplastic stroma.

B: An invasive gland within inflamed desmoplastic stroma shows marked nuclear atypia. Columnar cells have abundant eosinophilic cytoplasm.

C: Glandular cells have enlarged atypical nuclei, occasional nucleoli, and abundant cytoplasm, with one evident mucin vacuole.

Endometrial carcinoma may extend to the endocervix, but when it does, it usually has invaded the myometrium of the corpus and has become sufficiently bulky to enlarge the uterus. Primary adenocarcinoma of the endocervix tends to expand the cervix, so if it, rather than the corpus, is enlarged, an endocervical primary site is clinically suggested. Mucinous differentiation suggests origin in the cervix, but may occur in endometrial carcinoma as well. Bland squamous differentiation within an adenocarcinoma favors an endometrial primary site because squamous differentiation in endocervical adenocarcinomas is usually higher grade in appearance. The presence of AIS or HSIL also supports a primary endocervical origin. Immunohistochemical markers useful in the distinction are discussed above.

Treatment and Prognosis. The prognosis and survival rates of women with adenocarcinoma and squamous carcinoma of the cervix are essentially the same (21,36,37,93,217,238, 278,371,420) and both tumors are treated the same, stage for stage. The stage, size, histologic grade, depth of invasion, and presence or absence of lymph node metastases correlate with survival in most reports (238,323,398), although the evidence for a role for histologic grade is less convincing. Stage for stage, patients with low-ploidy or diploid tumors have a better prognosis than those with high-ploidy or aneuploid tumors (117). Lymphatic space involvement is an unfavorable finding (348), as tumors less than 1 cm have metastasized to lymph nodes (323,371).

Lymph node metastasis occurs in about 20 percent of patients with adenocarcinoma visibly confined to the cervix at operation (stage I), so radical hysterectomy and pelvic lymphadenectomy are appropriate for early stages (stages IB and IIA). Small, early-stage adenocarcinomas can be treated equally well by irradiation or hysterectomy (323). Hysterectomy is advantageous for bulky lesions as it is more difficult to destroy these by irradiation alone (278,323). Examination of pelvic lymph nodes identifies patients at high risk for recurrence and in need of postoperative radiation. Autopsy study of fatal cases suggests a higher rate of metastasis to the adrenal gland and paraaortic lymph nodes than in fatal cases of squamous cell carcinoma (101). Outside of the pelvis, the most common sites of metastasis are intraabdominal peritoneum, paraaortic lymph nodes, lung, and pleura (167).

Mucinous Adenocarcinoma

Mucinous adenocarcinoma has three forms: endocervical type, intestinal type, and signet ring cell type. The endocervical type is characterized by cells with pale granular cytoplasm and basal nuclei resembling the cells of the endocervix (figs. 5-102–5-105). These tumors correspond, for the most part, to the usual type of endocervical adenocarcinoma (that is, they are high-risk HPV related) but have a greater degree of mucinous differentiation. These tumors may be entirely or partially papillary. In the intestinal type, the cells exhibit intestinal type differentiation, with goblet cells, and, in rare cases, argentaffin cells. The signet ring cell type rarely occurs in a pure form; signet ring cells are usually present as a minor component mixed with endocervical or intestinal patterns. Pure signet ring cell carcinoma should be evaluated for the possibility of metastasis from a primary gastrointestinal tract adenocarcinoma.

Endometrioid Adenocarcinoma

Endometrioid adenocarcinoma is a neoplasm that closely resembles the usual type of adenocarcinoma that arises in the endometrium (figs. 5-106, 5-107). As noted above, this tumor is sometimes difficult to separate from an endocervical type adenocarcinoma. In our experience, it accounts for no more than 10 percent of endocervical adenocarcinomas. It is more easily recognized if it not only resembles a typical adenocarcinoma of the endometrium, but if it also shows squamous differentiation. To qualify as an endometrioid carcinoma, the squamous component must be well differentiated. If the squamous cells are cytologically malignant, the tumor is designated *adenosquamous carcinoma.* This differs from the classification of endometrial adenocarcinomas containing a squamous component, which are termed "endometrioid adenocarcinoma with squamous differentiation" and then graded as well, moderately, or poorly differentiated based on the glandular component. Because adenosquamous carcinoma may have special clinical and pathologic characteristics, it is designated as a separate type of carcinoma. A *mucoepidermoid carcinoma* has been defined as a squamous carcinoma containing mucin (402).

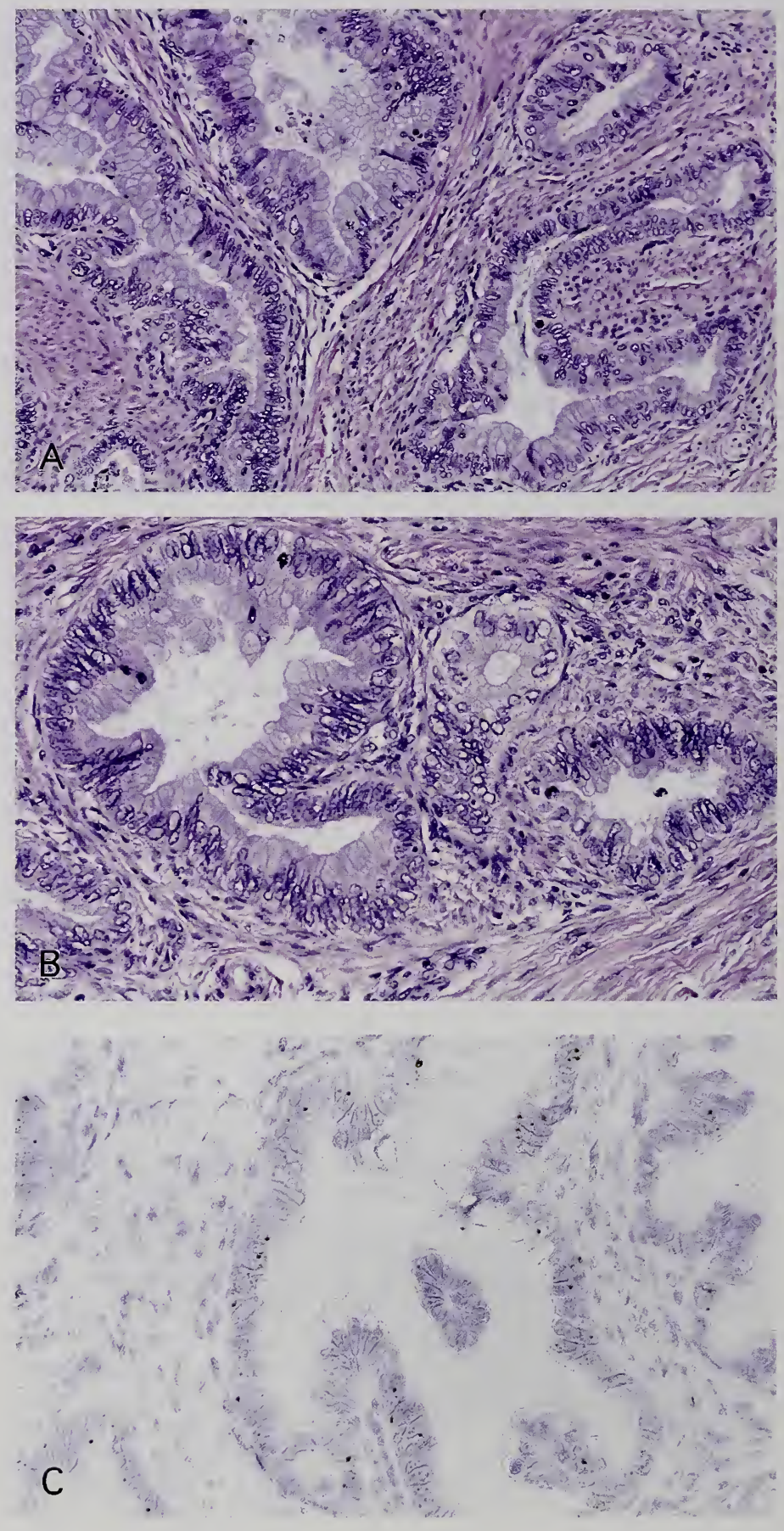


Figure 5-102

ENDOCERVICAL ADENOCARCINOMA, USUAL TYPE WITH MUCINOUS DIFFERENTIATION

A: The glands are composed of columnar cells with abundant pale mucinous cytoplasm and basally situated nuclei, reminiscent of normal endocervical glands.

B: Glands are well differentiated and have abundant mucinous cytoplasm but nuclear atypia is notable and mitotic activity is present (these cytologic features are distinctive from those seen in minimal deviation adenocarcinoma; see fig. 5-113).

C: In situ hybridization for HPV 16 demonstrates the punctate nuclear signals indicative of a positive result (in contrast, minimal deviation adenocarcinoma is generally negative for HPV).

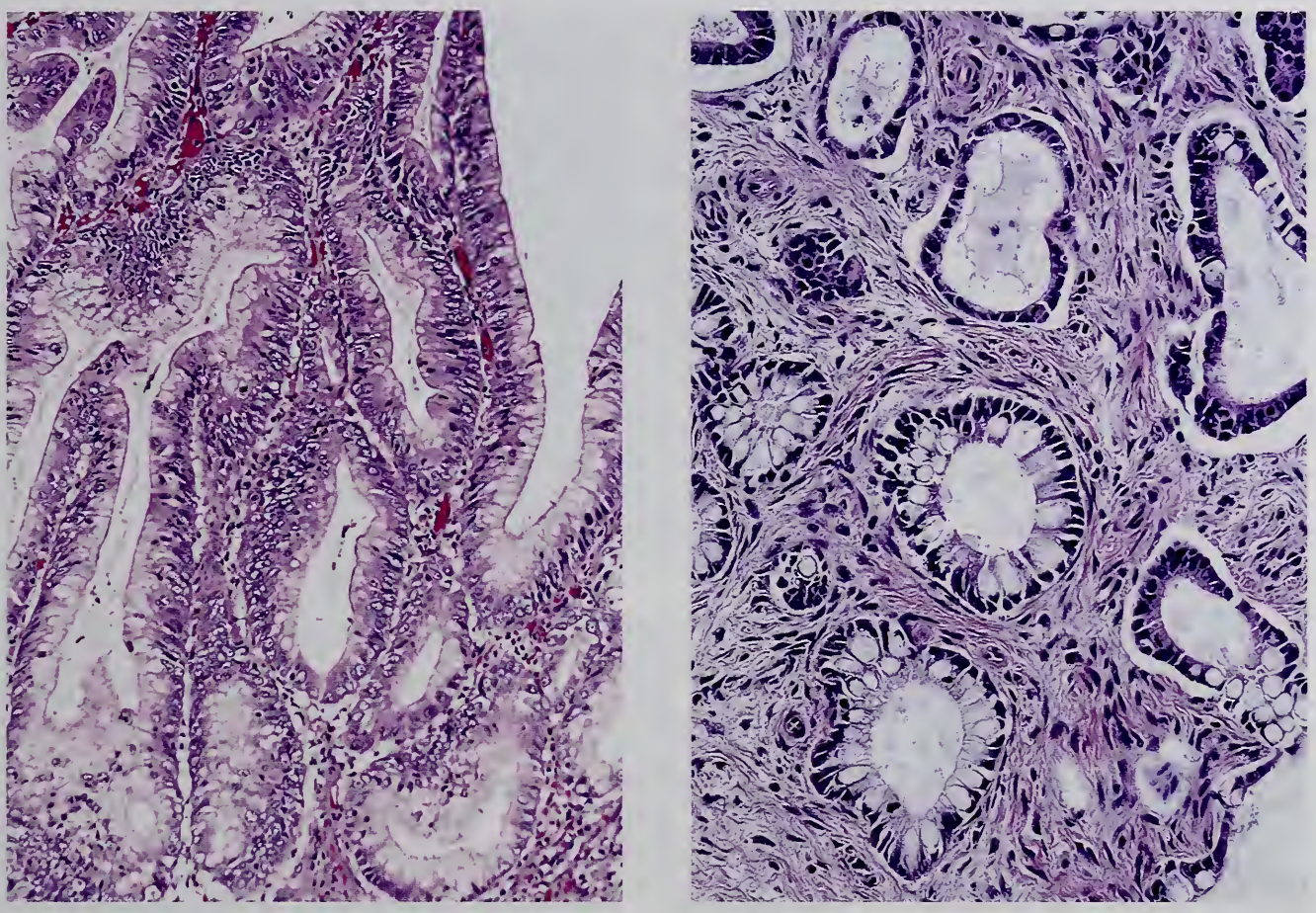


Figure 5-103

ENDOCERVICAL ADENOCARCINOMA, MUCINOUS INTESTINAL TYPE

The glands have abundant mucinous cytoplasm with columnar goblet cells.

Well-Differentiated Villoglandular Adenocarcinoma

Definition. *Well-differentiated villoglandular adenocarcinoma* is a well-differentiated carcinoma with a papillary architecture resembling villoglandular adenomas of the colon and the analogous primary endometrial adenocarcinoma.

General Features. Well-differentiated villoglandular adenocarcinoma is a clinically and pathologically distinctive tumor characterized by complex branching papillary processes. It is found in young women and has an excellent prognosis. None of the 37 reported cases have extended outside the uterus (193,441). Despite the lack of spread beyond the uterus thus far, well-differentiated villoglandular adenocarcinoma may be deeply invasive and extend to the endometrium. Most patients are less than 40 years old and some are less than 30 years old. Patients have signs and symptoms similar to those of patients with stage I adenocarcinoma of the cervix.

Gross Findings. Well-differentiated villoglandular adenocarcinoma usually appears as a polypoid or broad-based papillary protuberance resembling a polyp. Some tumors are more subtle, and appear as eroded or friable nodular enlargements.

Microscopic Findings. The neoplasm exhibits a complex branching or arborescent pattern resembling an exaggeration of normal surface endocervical papillary fronds and crypts. The papillary fronds may be thin or thick, with large branching papillae that give rise to smaller branching processes (figs. 5-108–5-110). Invasive portions are a continuation of the elongated branching glands separated by fibrous stroma. Stratified columnar cells that contain only sporadic mucinous cells usually line the papillary processes. Pseudostratification of the cells

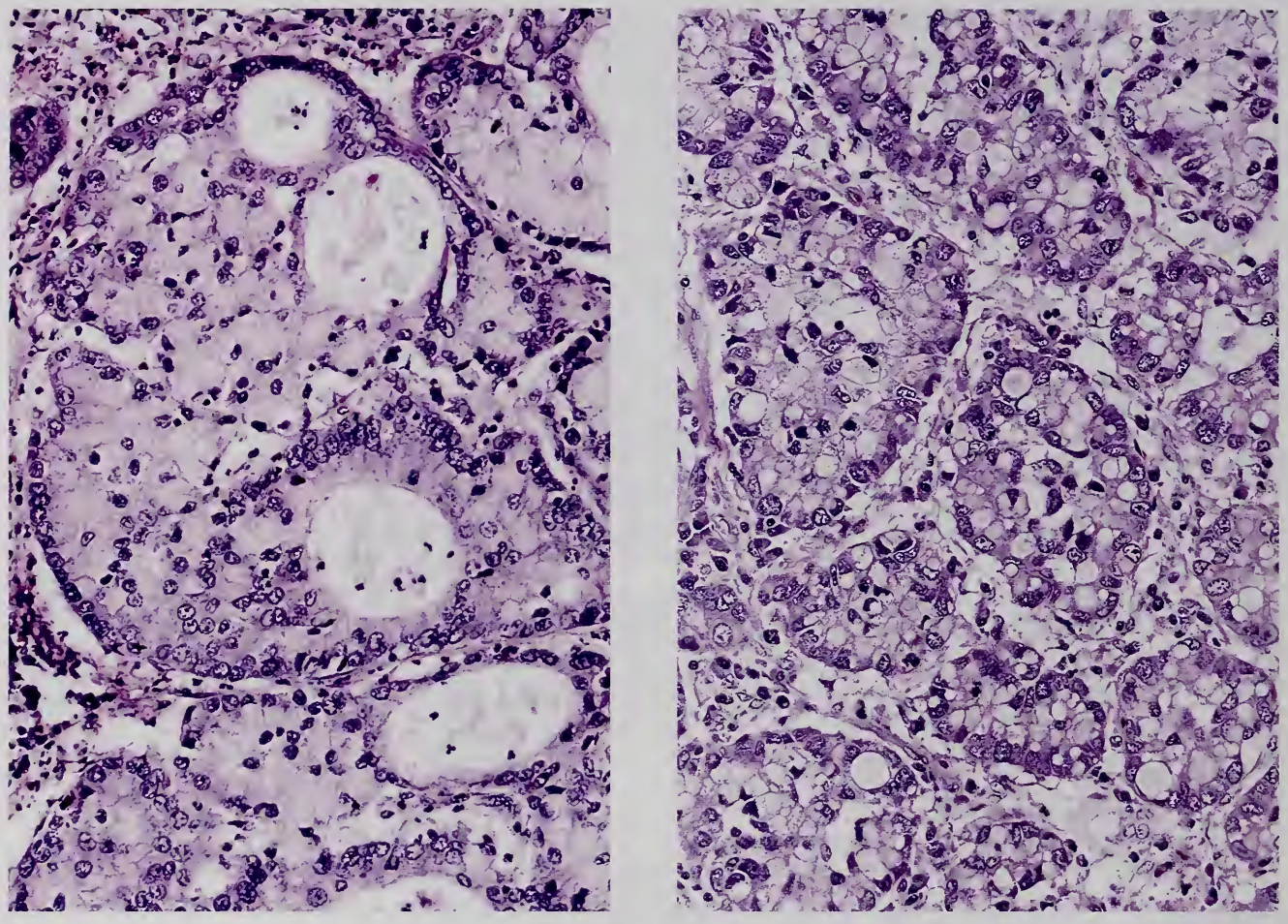


Figure 5-104

ENDOCERVICAL ADENOCARCINOMA, MUCINOUS TYPE WITH SIGNET RING CELL DIFFERENTIATION

Left: Mucinous glands are partially filled with cells having signet ring cell features.
Right: Some cells have columnar features but most of the cells in the aggregates exhibit signet ring cell differentiation.

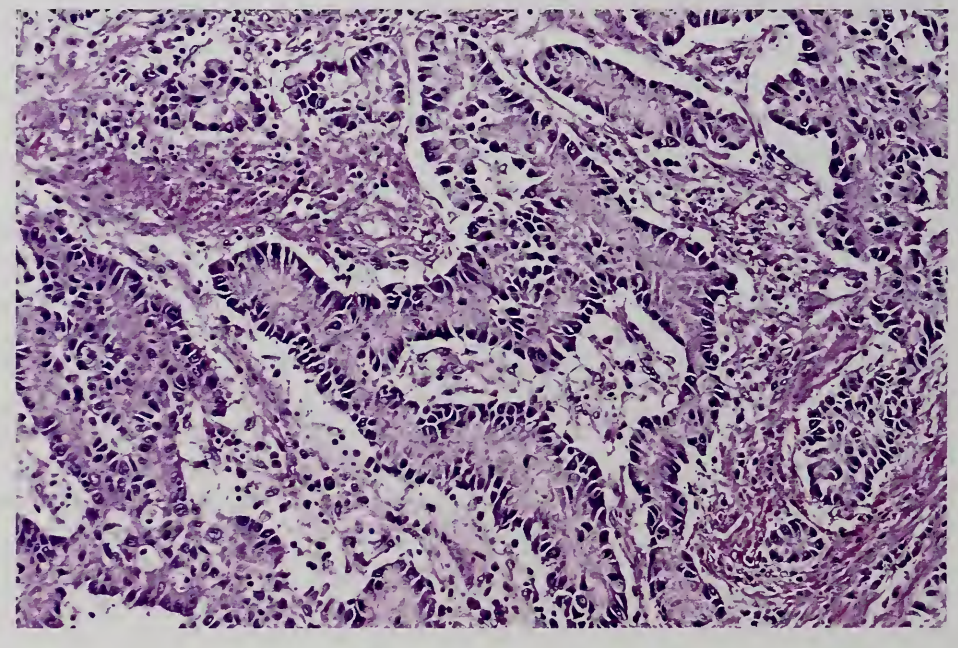


Figure 5-105

ENDOCERVICAL ADENOCARCINOMA, MUCINOUS TYPE

The cords of tumor with abundant mucinous cytoplasm impart a sertoliform pattern.

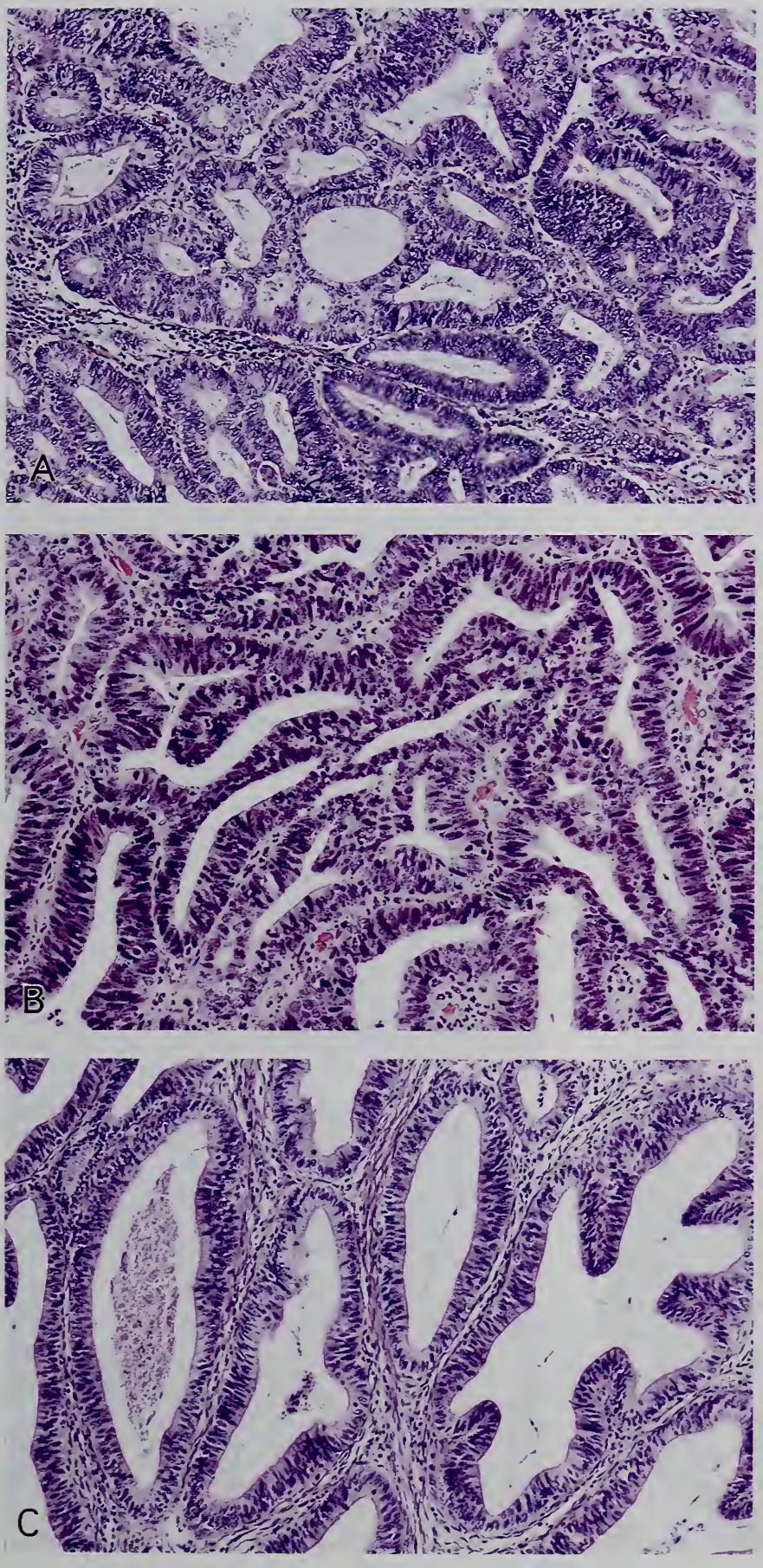


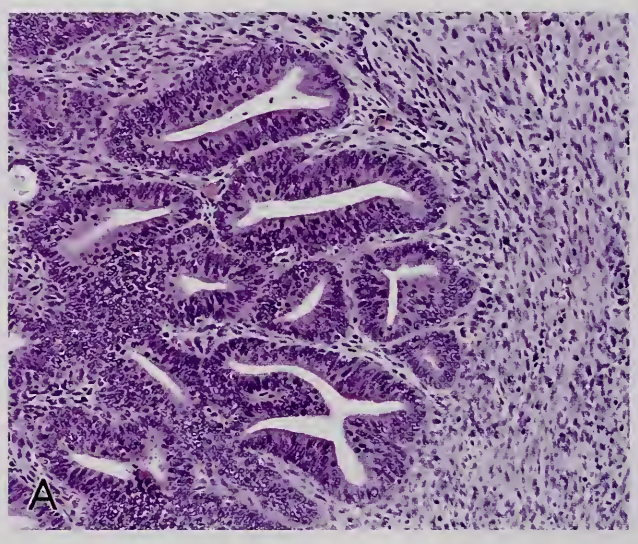
Figure 5-106

ENDOCERVICAL ADENOCARCINOMA, ENDOMETRIOID VARIANT OF USUAL TYPE

A: The tumor exhibits glandular and cribriform growth. The glands have columnar cells with limited mucinous cytoplasm, simulating endometrioid carcinoma of the endometrium.

B: Confluent glandular epithelium contains cells with columnar hyperchromatic nuclei and greatly diminished mucinous cytoplasm, simulating endometrioid carcinoma of the endometrium.

C: Well-differentiated glands with columnar nuclei and diminished mucinous cytoplasm simulate endometrioid carcinoma of the endometrium.



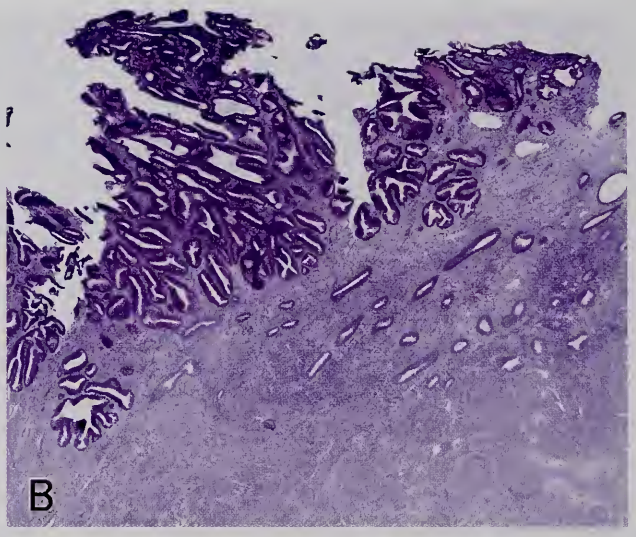


Figure 5-107

ENDOCERVICAL ADENOCARCINOMA, ENDOMETRIOID TYPE

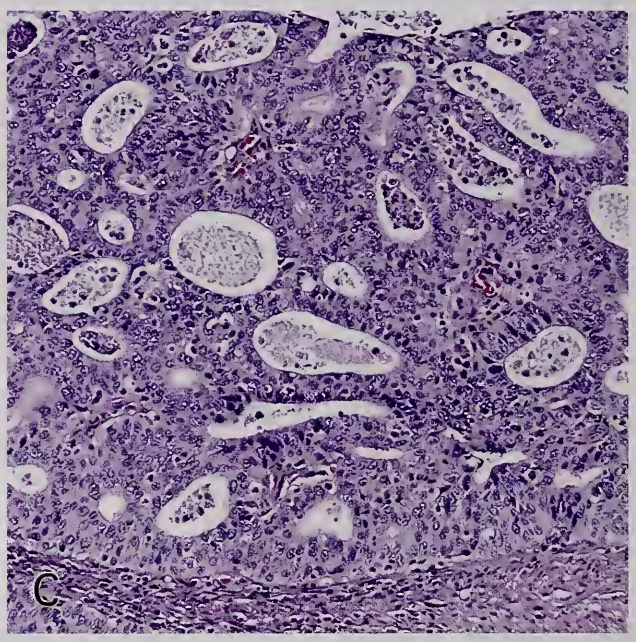
A: Extension of individual glands into the endometrium, with little stromal reaction, simulates complex atypical endometrial hyperplasia.

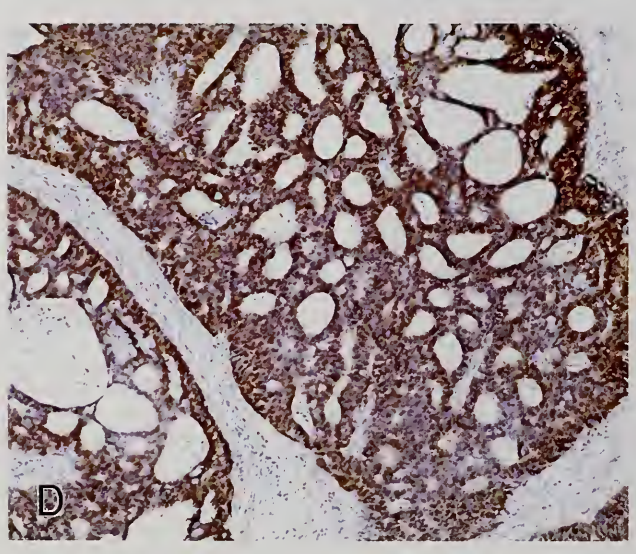
B: Extension of endocervical carcinoma into the endometrium of the lower uterine segment simulates complex endometrial hyperplasia, which can lead to misclassification of the adenocarcinoma as endometrial rather than endocervical in origin.

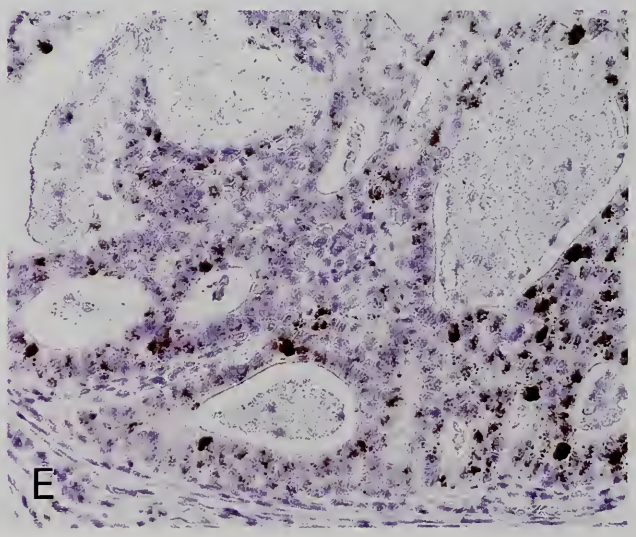
C: Cribriform endometrioid pattern simulates primary endometrial endometrioid carcinoma.

D: Diffuse expression of p16 characterizes HPV-related endocervical adenocarcinomas and distinguishes them from endometrial endometrioid carcinomas which exhibit patchy expression of p16 (same example as C).

E: In situ hybridization demonstrating the presence of HPV 16 establishes that the adenocarcinoma is of endocervical rather than endometrial origin (same example as C).







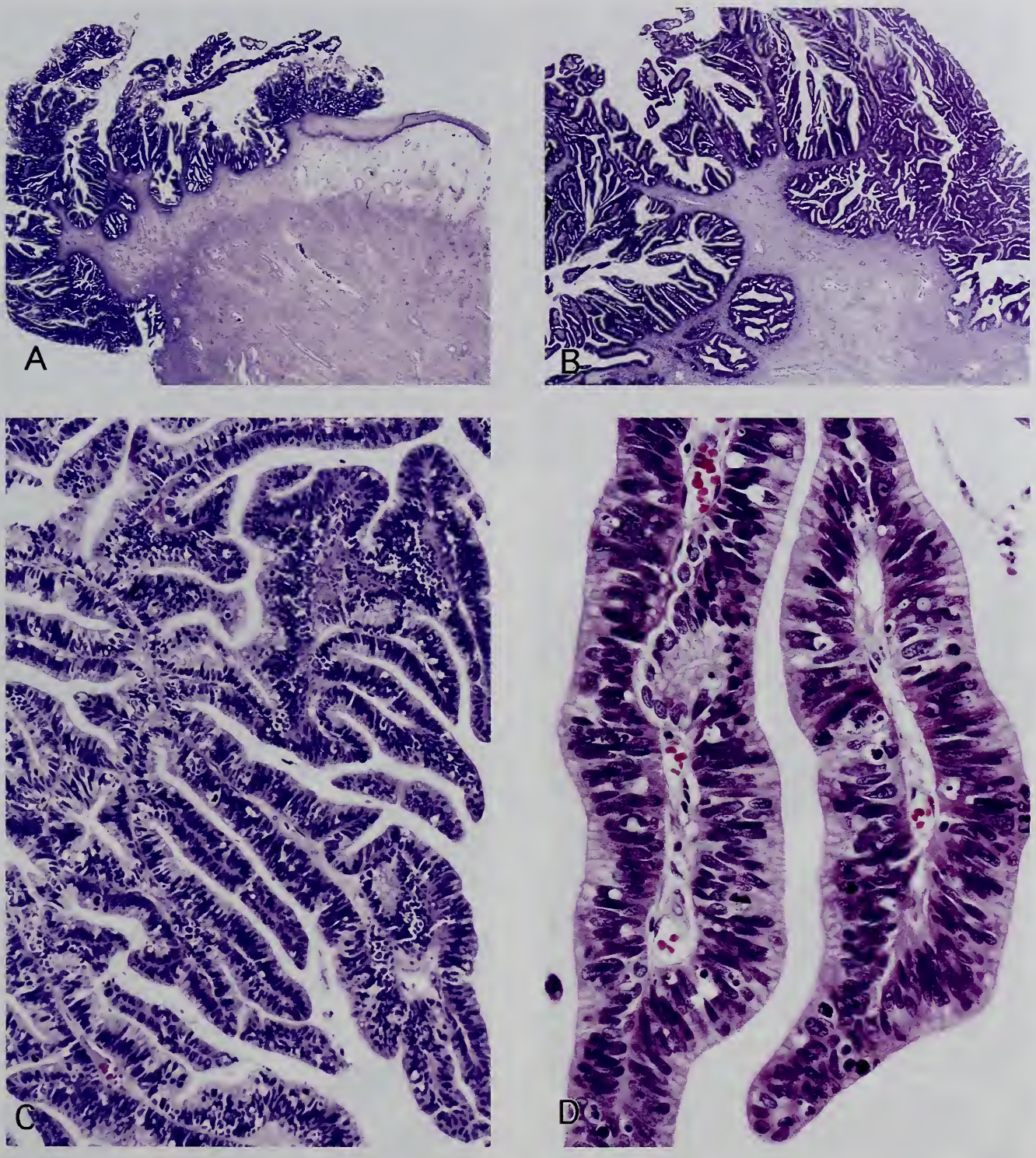


Figure 5-108

ENDOCERVICAL ADENOCARCINOMA, WELL-DIFFERENTIATED VILLOGLANDULAR ENDOMETRIOID/USUAL TYPE

A: An exophytic tumor emanating from the cervical transformation zone mucosa does not invade underlying cervical stroma.

B: Villoglandular growth is sufficiently complex to represent an exophytic adenocarcinoma. Two rounded nests of tumor cells in the superficial stroma may indicate focal stromal invasion but could represent tangentially sectioned complex glandular growth at the base of the tumor.

C: Long villous structures have a predominantly endometrioid appearance at low to intermediate magnification.

D: Higher magnification reveals "usual type" differentiation, a hybrid of mucinous and endometrioid differentiation, as well as numerous mitotic figures and apoptotic bodies which are characteristic of HPV-related endocervical adenocarcinomas.

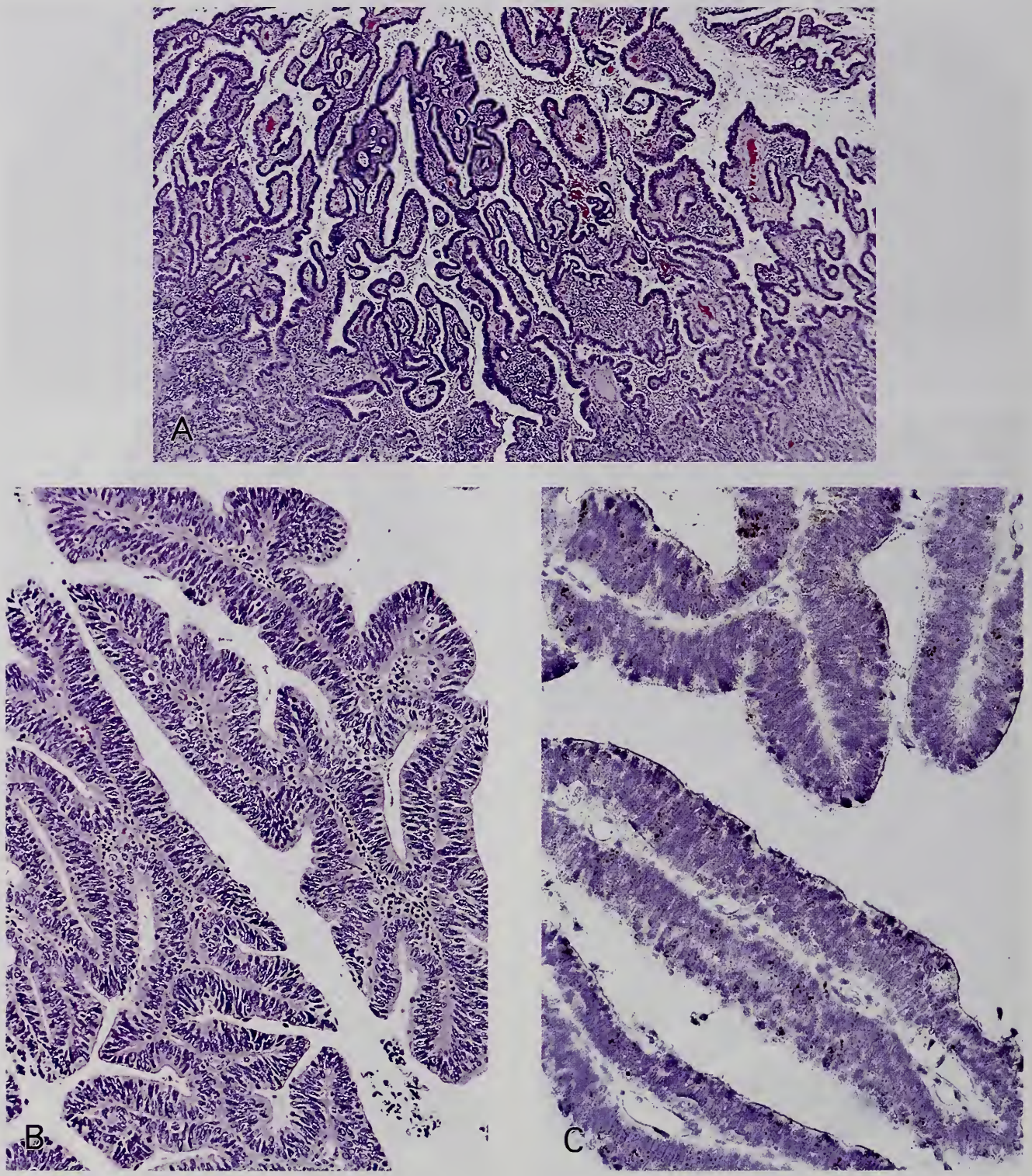


Figure 5-109

ENDOCERVICAL ADENOCARCINOMA, WELL-DIFFERENTIATED VILLOGLANDULAR ENDOMETRIOID VARIANT OF USUAL TYPE

A: Complex villoglandular growth is predominantly exophytic.

B: Villous structures have elongated nuclei and greatly diminished mucinous cytoplasm, similar to endometrioid carcinoma of the endometrium.

C: The presence of HPV is characteristic of villoglandular endocervical adenocarcinomas; in this case, in situ hybridization demonstrates the presence of HPV 16.

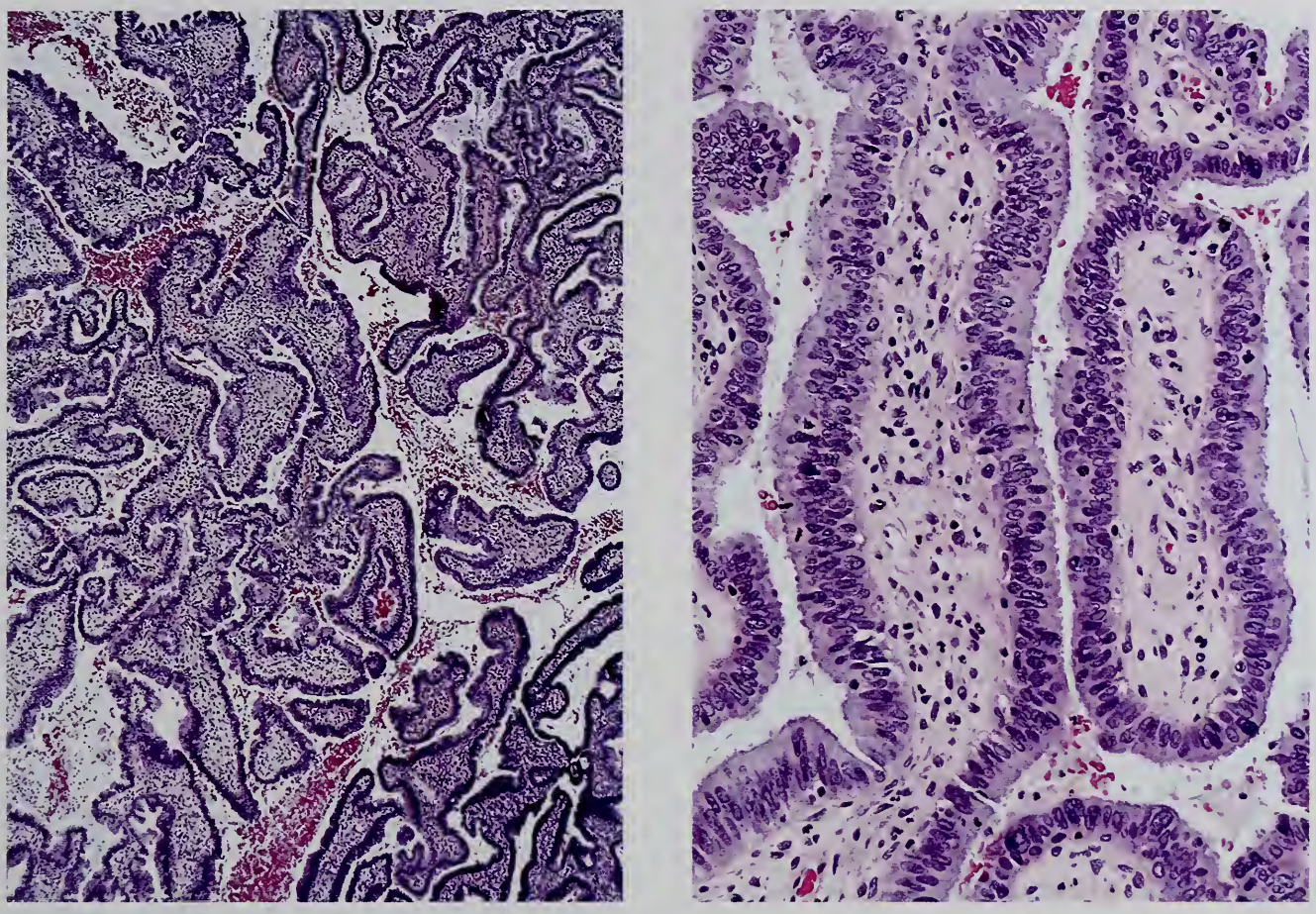


Figure 5-110

ENDOCERVICAL ADENOCARCINOMA, WELL-DIFFERENTIATED VILLOGLANDULAR MUCINOUS VARIANT OF USUAL TYPE

Left: A complex glandular proliferation forms numerous broad papillae, consistent with a villoglandular pattern. Right: Papillae are lined by mucinous epithelium with notable nuclear atypia and numerous mitotic figures.

in a single layer is common. Typically, there is low-grade cytologic atypia. The cells lining the fronds are usually endometrioid in type but can be endocervical or intestinal. The stroma may be desmoplastic or myxoid at the advancing margin. AIS of the endocervix frequently occurs in association with this neoplasm.

It is extremely important to restrict the diagnosis of well-differentiated villoglandular adenocarcinoma to papillary tumors that have low-grade cytologic atypia and that are pure. Conventional adenocarcinomas can be papillary but they display greater cytologic atypia and mitotic activity. Well-differentiated villoglandular carcinomas with areas of conventional endocervical carcinoma that have spread to regional lymph nodes have also been reported, including one in a patient who died, underscoring the importance of restricting the diagnosis to pure well-differentiated villoglandular carcinomas (197). Most studies indicate that this villoglandular variant contains high-risk HPV DNA (15,190,258,320).

Differential Diagnosis. Other papillary carcinomas (serous, mucinous, and clear cell types) have smaller papillae that form a more complex lattice. The cells in these latter tumors display much more marked nuclear atypia and a much higher mitotic index in contrast to well-differentiated villoglandular adenocarcinoma. Superficial well-differentiated villoglandular carcinomas are difficult to distinguish from papillary endocervicitis, papillary adenofibroma, and müllerian papilloma. All three of these lesions have less nuclear atypia than villoglandular adenocarcinomas. In areas where invasion is equivocal, the cells lining the processes should be cytologically malignant.

Treatment and Prognosis. In two series specifically devoted to villoglandular adenocarcinoma, the tumor was superficially invasive in the majority of cases (193,441); in three women there was deep invasion. One of the deeply invasive lesions extended to the endometrium, and invaded the myometrium apart from its origin in the endocervix.

A conization is likely to be curative if the margins of the cone are free of tumor, invasion is no more than 3 mm, there is no vascular space invasion, and the tumor is pure. Conservative therapy is advocated for superficially invasive lesions because none have metastasized and there has been no association with coexistent ovarian tumors (193,441).

Endocervical Adenocarcinoma, Microcystic Type

Endocervical adenocarcinoma, microcystic type is a variant of endocervical adenocarcinoma, usual type, in which the glands form variably sized cysts with attenuated epithelium (fig. 5-111). This tumor simulates benign glandular lesions and minimal deviation adenocarcinoma (434).

Clear Cell Carcinoma

Definition. *Clear cell carcinoma* is an adenocarcinoma that is composed mainly of clear or hobnail cells arranged in a tubulocystic, papillary, solid, or combination pattern.

General Features. Clear cell carcinoma accounts for about 4 percent of adenocarcinomas of the cervix (294). Almost two thirds of cases have occurred in women exposed in utero to DES or a related substance. Clear cell carcinoma of the cervix also develops in the absence of in utero DES exposure, as demonstrated by its occurrence in women born before the use of DES during pregnancy (198). Of the cervical tumors related to DES exposure, about 50 percent are associated with vaginal adenosis and about 20 percent with gross structural cervicovaginal mesenchymal abnormalities such as hypoplasia, strictures, bands, fibroepithelial polyps, and malformations of the cervicovaginal interface (337). Chapter 6 discusses these tumors in more detail.

Gross Findings. Clear cell carcinomas vary from everting nodular reddish lesions to small punctate ulcers (198,337).

Microscopic Findings. Papillary, tubulocystic, and solid patterns occur in clear cell carcinomas of the cervix. The cells have clear or eosinophilic granular cytoplasm, and often have a hobnail shape. Hobnail cells have prominent nuclei but scant cytoplasm so that the nucleus appears to protrude into the lumen of neoplastic tubules and cysts. The tubules are typically lined by a single layer of bland cells (fig. 5-112). The microscopic features are the same as in clear cell carcinoma of the vagina. As in the vagina, the tumors are closely associated with vaginal adenosis or with tuboendometrial glands in the exocervix (cervical ectropion).

Differential Diagnosis. Some squamous cell carcinomas are composed of clear cells that contain abundant glycogen, but glands and tubules are not present. Among benign lesions, the differential diagnosis includes microglandular hyperplasia, Arias-Stella reaction, and mesonephric remnants. Microglandular hyperplasia tends to be polypoid, with small markedly crowded glands lined by a single layer of bland cuboidal cells and usually accompanied by squamous metaplasia. If sheets of clear cells are formed in microglandular hyperplasia, the small bland nuclei and low mitotic activity should distinguish it from clear cell carcinoma. Adenosis and ectropion, stigmata of DES exposure in utero, are rarely associated with microglandular hyperplasia but are common with clear cell carcinoma. Arias-Stella reaction occurs with intrauterine or ectopic pregnancy and gestational trophoblastic disease. In the Arias-Stella reaction, the nuclei are focally enlarged and have hyperchromatic smudged chromatin; mitotic figures are absent (see Arias-Stella Reaction). The glands are secretory and the cells are distended by secretory vacuoles; they do not contain the granular or eosinophilic cytoplasm seen in clear cell carcinoma. There may be an associated decidual change in the cervical stroma near the glands showing an Arias-Stella reaction. Mesonephric remnants tend to be clustered deep in the lateral wall of the cervix, below the level of the endocervical glands, and are often arranged around a central duct. They are not associated with adenosis, and there is no surface ulceration or cervicovaginal mesenchymal abnormalities as in clear cell carcinoma.

Treatment and Prognosis. More than 85 percent of clear cell carcinomas are stage I or II when detected (337). Treatment is either radical hysterectomy and vaginectomy or radiation. Metastasis occurs to pelvic nodes in about 18 percent of patients with stage I disease, but the frequency of metastasis reaches nearly 50 percent for those with stage II tumors (337).

The survival rate of patients with stage I disease is about 90 percent. Most recurrences are seen within 3 years of initial treatment. Metastases more often involve distant sites than with squamous cell carcinoma: 36 percent of initial recurrences are to the lungs or supraclavicular nodes in contrast to less than 10 percent in patients with squamous cell carcinoma. Features that are associated with a better prognosis include small tumor size, shallow depth of invasion (194), older age of the patient (over 19 years), a tubulocystic microscopic pattern (337), and lesser degrees of nuclear atypia (158).

Minimal Deviation Adenocarcinoma

Definition. *Minimal deviation adenocarcinoma* (MDA) is a rare, highly differentiated adenocarcinoma in which many of the glands are impossible to distinguish cytologically from normal ones. *Adenoma malignum* is a synonym.

General Features. MDA is an unusual, very well-differentiated adenocarcinoma in which the cells lining the glands lack cytologic features of malignancy (375). Although when first reported, all the tumors were mucinous carcinomas, more recently, MDA has been expanded to include endometrioid and clear cell variants. This neoplasm has probably received more attention than it deserves, as it is extremely rare and probably accounts for only 1 percent of cervical adenocarcinomas based on a study of 389 cases from the Armed Forces Institute of Pathology (200). In our experience and that of others (433), most cases of suspected MDA referred for consultation are rarely confirmed. The vast majority are either benign glandular proliferations or normal, slightly irregular glands that are deeper than usual. The rarity of MDA is attested to by the absence of a single case in a population-based study from over a 4-year period (13). Nonetheless, MDA does occur and can appear deceptively innocuous.

As with ordinary adenocarcinoma, a mucoid or watery vaginal discharge is common. Abnormal cervical glandular cells are evident in smears from most cases (196,393). More than any other type of cervical adenocarcinoma, MDA, particularly the mucinous form, is more likely to coexist with an ovarian neoplasm (200,444), usually a mucinous neoplasm or a rare ovarian sex cord stromal tumor with annular tubules (SCTAT) (264,444). Both MDAs and SCTAT tumors are strongly associated with the Peutz-Jeghers syndrome (264).

Gross Findings. MDA may be ulcerative or polypoid, but often it forms a suspicious-appearing irregularity or the cervix is stenotic without an evident mucosal lesion. With early lesions the cervix may appear normal (130,200).

Microscopic Findings. MDA is identified by the presence of cytologically bland glands with irregular, angulated contours that vary in size and shape; a desmoplastic response; increased mitotic activity; and an increased number of glands displaying a haphazard pattern of infiltration, positioned deeper than the lower level of normal endocervical glands. Normal glands seldom extend more than 5 mm below the endocervical surface, but on occasion, they are found deeper in the cervix. In nearly all instances, the diagnosis of MDA cannot be made reliably on biopsy material because deeply positioned glands confirm the presence of invasion, and a deep conization or hysterectomy specimen is needed (130).

Characteristically, the glands vary in size, ranging from small and round to large, irregular, and distorted forms with angular projections, often displaying unusual branching patterns and papillary infoldings. *Mucinous MDA* is the most common form of MDA. In this carcinoma, the glands are lined by a single layer of columnar mucin-producing cells resembling the cells of endocervical glands. Some or even many of the glands appear normal except for their shape. Peculiar elongation or branching processes are common. In some glands, the nuclei are basal, with little or no atypia and inconspicuous nucleoli. Some glands, however, particularly smaller, deeply infiltrative ones, exhibit nuclear atypia characterized by slightly enlarged vesicular nuclei with prominent red nucleoli (figs. 5-113, 5-114).

MDA may also display an endometrioid or nonspecific cellular type of differentiation. In

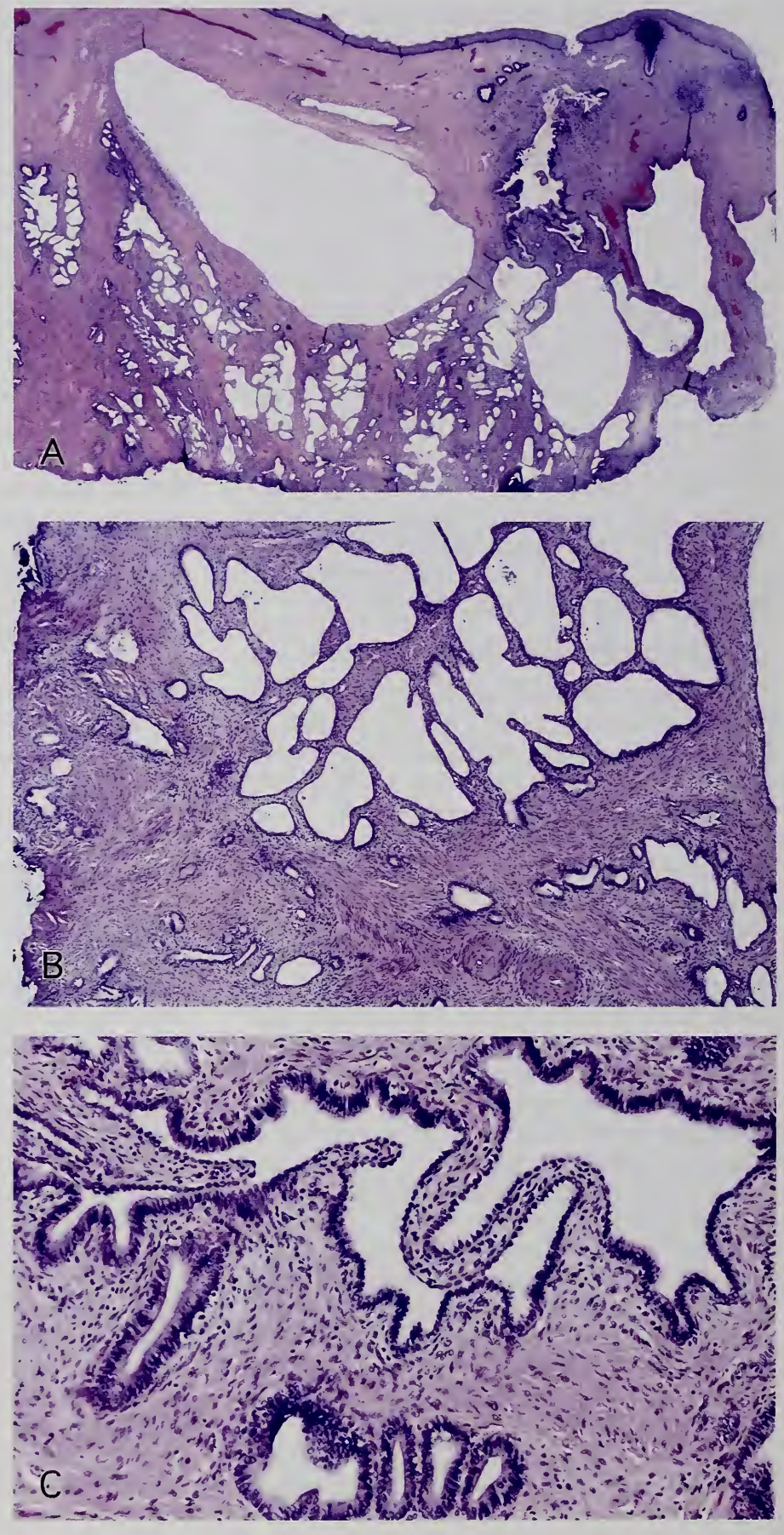


Figure 5-111

ENDOCERVICAL ADENOCARCINOMA, MICROCYSTIC VARIANT OF USUAL TYPE

A: Variably sized clustered and dilated glands extend deep into cervical stroma (figs. A thru F are from the same lesion).

B: Clustered dilated glands and small infiltrative glands fill the cervical stroma and extend to the margin.

C: Irregularly branching glands are lined by endometrioid type epithelium and surrounded by nonreactive stroma.

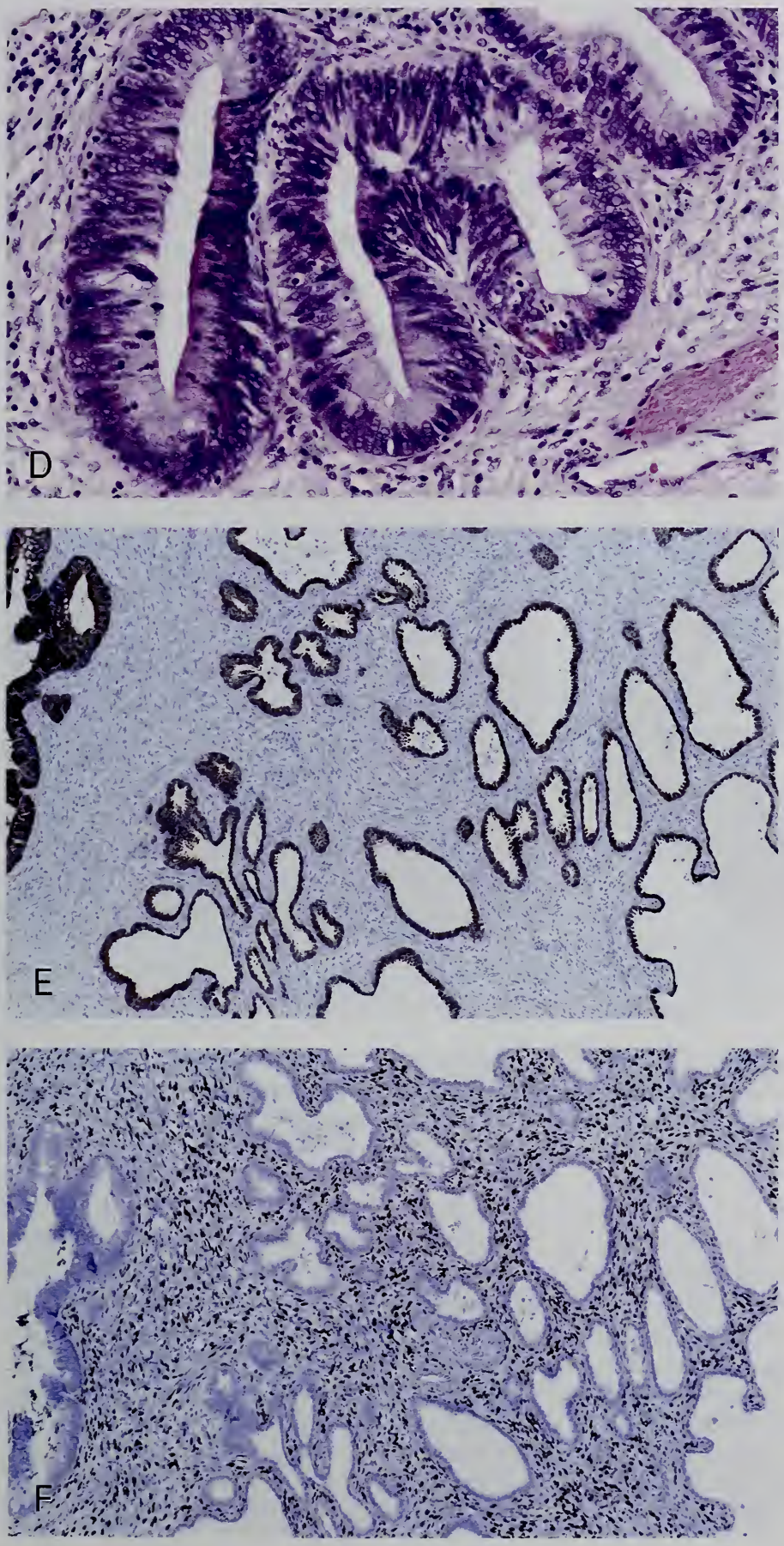


Figure 5-111 (Continued)

D: Small noncystic glands exhibit the characteristic hybrid endometrioid and mucinous differentiation, nuclear atypia, and mitotic activity of an HPV-related adenocarcinoma.

E: Diffuse expression of p16 correlates with the presence of high-risk HPV, indicating an HPV-related type of adenocarcinoma.

F: Lack of hormone receptor expression (progesterone receptor [PR] is illustrated; both estrogen receptor [ER] and PR were negative) is characteristic of an HPV-related adenocarcinoma (normal stroma serves as internal positive control).

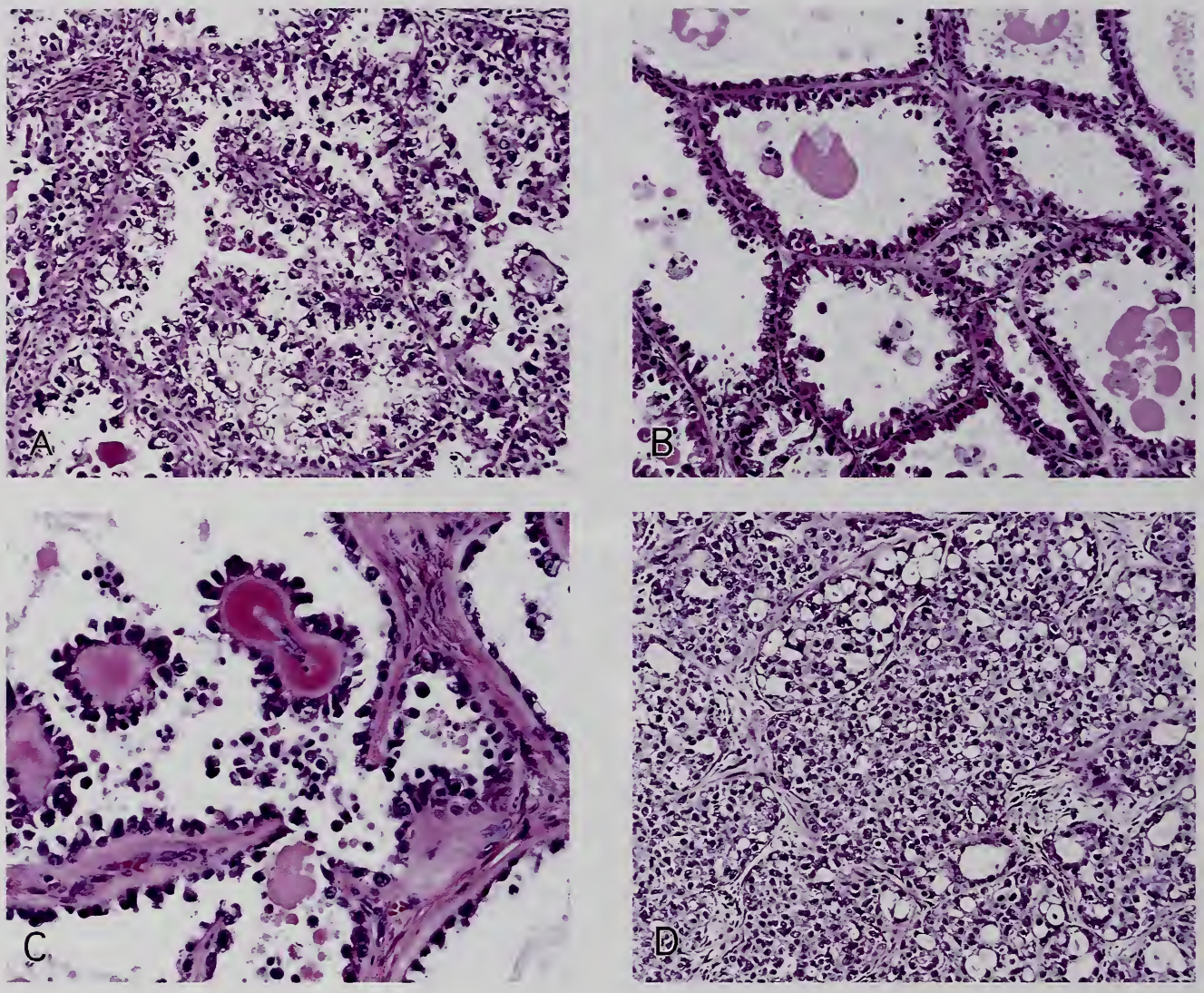


Figure 5-112

CLEAR CELL CARCINOMA

A: Glands are lined by characteristic hyperchromatic hobnail cells.
B: Dilated glands are lined by hobnail cells with hyperchromatic nuclei.
C: Papillae with central hyaline fibrous tissue cores are lined by hobnail cells with hyperchromatic nuclei.
D: Nests of tumor with a predominantly solid pattern are composed of cells with clear to pale eosinophilic cytoplasm, notable nuclear atypia, focal gland formation, and variably sized cytoplasmic vacuoles, simulating signet ring cell differentiation.

endometrioid MDA, the tumor cells resemble those of proliferative endometrium or endometrial hyperplasia. In *MDA with nonspecific cellular features*, the glands are small and uniform, with gaping lumens often containing homogeneous hyaline material. Although most of the cells lining the glands are bland, a careful search discloses some that are clearly atypical (fig. 5-115). In the absence of some glands exhibiting nuclear atypia, MDA should probably not be diagnosed.

Immunohistochemical Findings. MDA is highly variable in its staining for CEA. It is usually positive in focal areas, whereas well-differentiated cervical adenocarcinoma is usually more diffusely positive (404). All benign lesions tested to date, except for microglandular hyperplasia, are negative for CEA (269,384). Immunostaining may help in some instances, but because of its variable pattern in MDA, the results must be interpreted cautiously.

Recent studies have demonstrated that gastric mucins are expressed in 2 to 8 percent of normal glands compared to 95 percent of MDA lesions (171,272). Some MDAs are associated with lobular endocervical glandular hyperplasia (LEGH) and both of these lesions frequently express markers of gastric differentiation, suggesting a relationship (272). ER and PR are generally not expressed in MDA but are present in normal endocervical glands (273,404). CA125 is decreased in MDA compared to normal endocervical glands. MDAs also uncommonly express p16 (272) and most studies indicate that MDA is unrelated to high-risk HPV infection (15,107,320,405). This is consistent with the finding that p53 is expressed in the majority of MDAs (69), unlike most HPV-related cervical adenocarcinomas, which are negative due to the interaction of high-risk HPV E6 with p53. Thus, hormone receptors and p53 but not p16 may be of value in distinguishing MDA from benign endocervical glandular proliferations.

Differential Diagnosis. Deeply positioned Nabothian cysts, nodular clustering of normal endocervical glands (see section on tunnel clusters), microglandular hyperplasia, and mesonephric hyperplasia are the major considerations in the differential diagnosis. Endocervical glands are normally confined to within 5 mm of the surface, but may nearly extend to the serosal surface. These differ from MDA by having a single layer of flat to cuboidal inactive-appearing bland cells (72). Nodular collections of endocervical glands, so-called tunnel clusters, differ from MDA since MDA has a greater variation in size, shape, and depth of its glands, and by the irregularity at its infiltrating margin. Microglandular hyperplasia differs from MDA in that it is more everting, polypoid, and superficial, and does not extend below the level of the endocervical glands. Microglandular hyperplasia also has greater crowding of glands, squamous metaplasia is usually present, and enlarged branching glands are absent. In contrast to mesonephric remnants and mesonephric hyperplasia, MDA lacks a lobular or clustered arrangement and the glands have more irregularly shaped outlines.

Other benign lesions that can be confused with MDA are intestinal metaplasia and AIS. Intestinal metaplasia, often seen with AIS, displays cytologic atypia and mitotic activity in excess of that found in MDA. Both intestinal metaplasia and AIS are limited in their extent and do not extend below the level of normal endocervical glands.

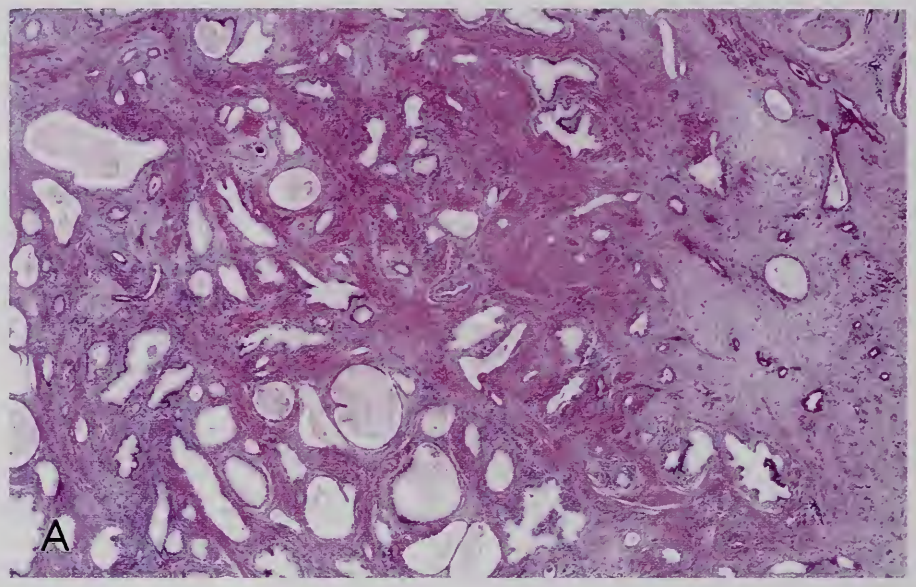
Treatment and Prognosis. Ideally, the therapy for MDA should be the same as for ordinary adenocarcinoma of the same stage, but the lesion is often not recognized before hysterectomy. The prognosis for patients with MDA is unsettled. Most studies, particularly the early ones, reported an unfavorable survival rate, but many of the neoplasms in these early studies were diagnosed in advanced stages (266). Also, many MDAs fail to form a visibly evident lesion despite deep infiltration, leading to greater opportunity for vascular invasion and clinical understaging. This results in undertreatment and a relatively poor prognosis. Some studies, however, report survival rates for patients with MDA as good as for other forms of well-differentiated adenocarcinoma of the cervix at the same stage (200,375). A majority of reports finds survival of patients with MDA an exception to the rule that a well-differentiated carcinoma has a better prognosis than a poorly differentiated one (130). The distribution of metastases is similar to that of ordinary forms of cervical adenocarcinoma (130).

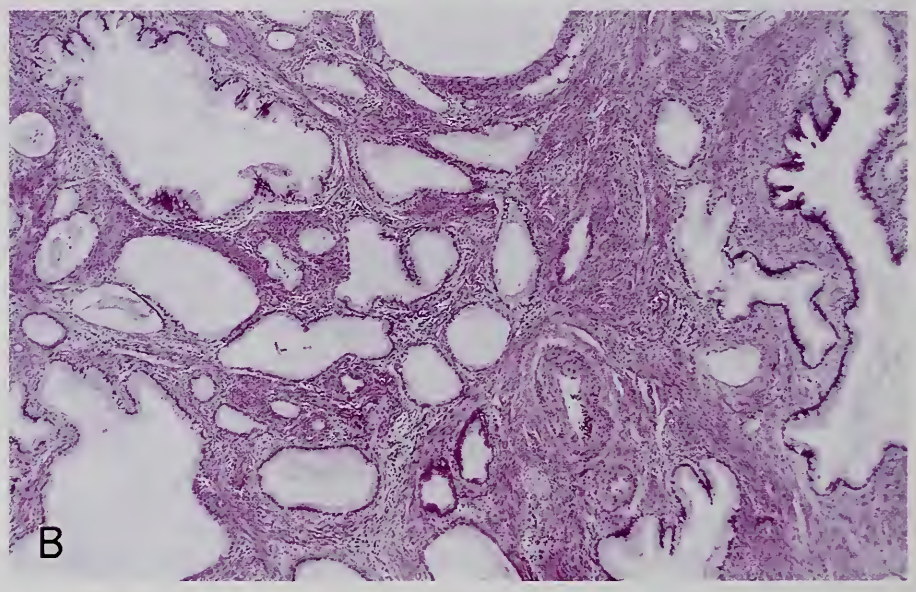
Serous Adenocarcinoma

Serous adenocarcinoma of the cervix is rare, representing less than 1 percent of cervical adenocarcinomas. It is identical to serous carcinoma of the endometrium. The tumor is characterized by complex papillae and slit-like glandular spaces lined by cells with pleomorphic high-grade nuclei. In the largest series thus far reported, survival did not differ significantly from that of the usual type of endocervical adenocarcinoma (450). As this study consisted of only 17 cases, we reserve judgment on this conclusion given the extremely poor prognosis of serous carcinomas in the endometrium, which have been much more extensively studied.

Mesonephric Adenocarcinoma

Carcinomas arising in mesonephric remnants of the cervix are extremely rare (29,74,411). Older reports confused *mesonephric carcinoma* with clear carcinoma. Carcinomas arising from





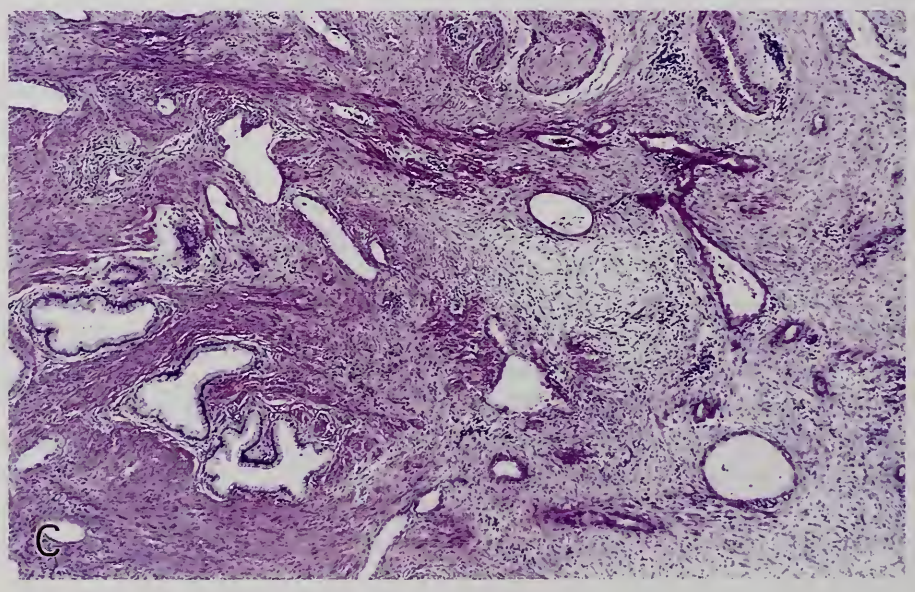


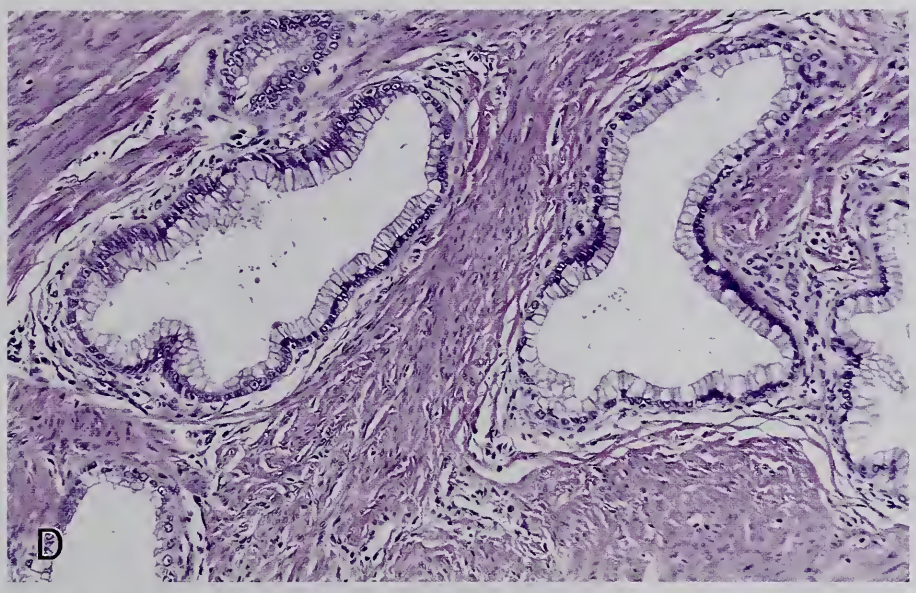
Figure 5-113

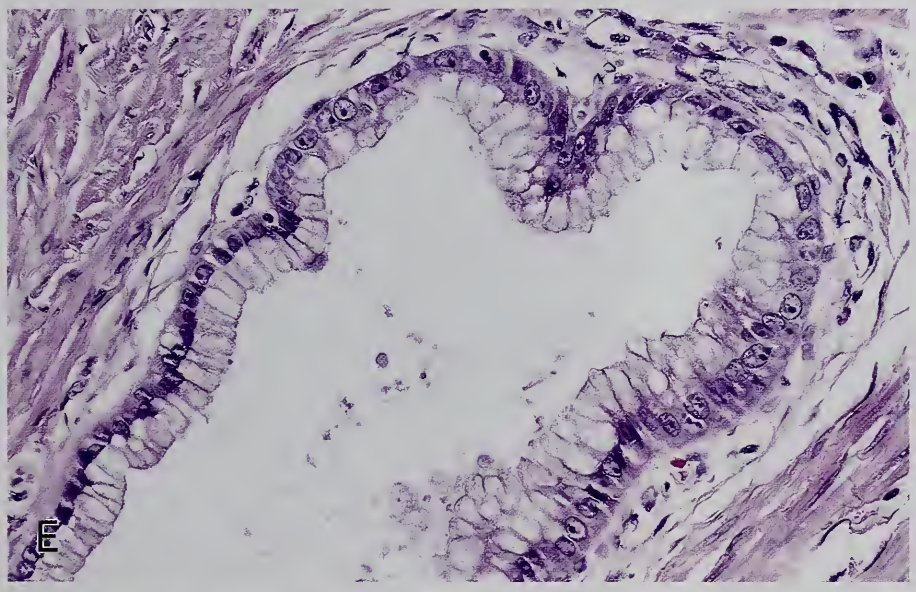
MINIMAL DEVIATION ADENOCARCINOMA, MUCINOUS TYPE

A: The glandular proliferation extends diffusely throughout the cervical stroma, which is predominantly densely eosinophilic and nonreactive, and only focally exhibits an edematous desmoplastic reaction in the deepest portion (figs. A thru F are from the same lesion).

B: Variably sized and shaped well-differentiated glands are surrounded by nonreactive stroma; some are in close proximity to thick-walled blood vessels.

C: Well-differentiated glands are surrounded by nonreactive stroma, whereas irregularly infiltrative glands are surrounded by edematous reactive stroma.





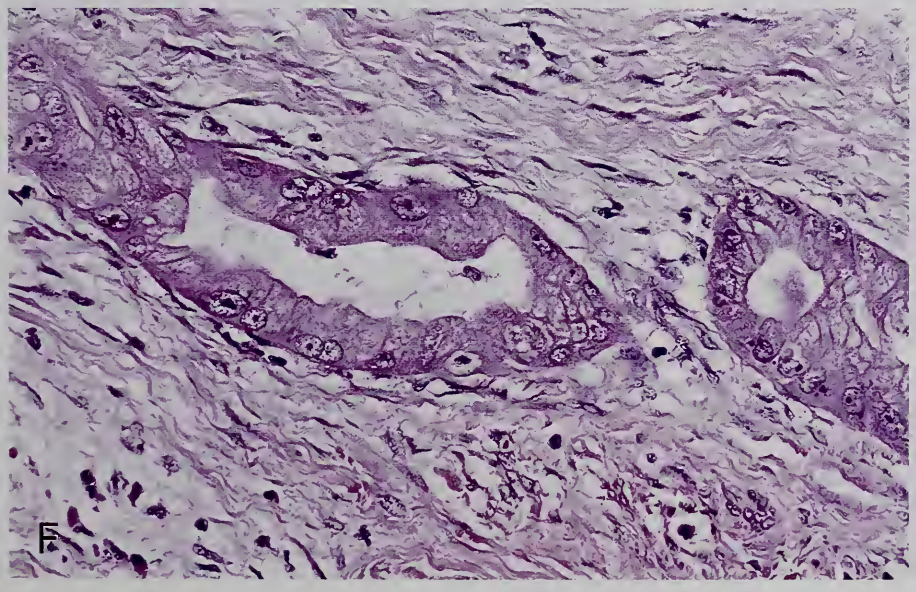
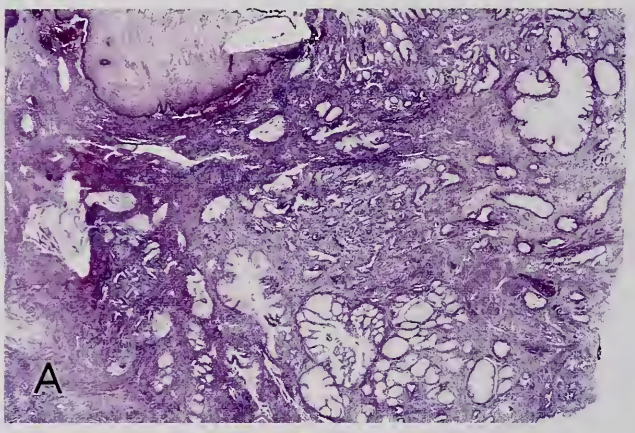


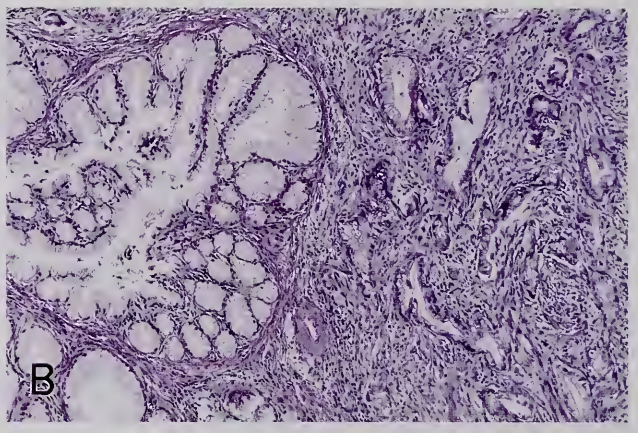
Figure 5-113 (Continued)

D: Well-differentiated glands are situated deeply in the cervix but exhibit minimal nuclear atypia and do not elicit a stromal reaction.

E: Higher magnification of the well-differentiated gland seen in figure D shows that while many of the nuclei exhibit little or no atypia, some do display the characteristic atypia of this type of adenocarcinoma, manifested as rounded nuclei with vesicular chromatin and prominent eosinophilic nucleoli.

F: Despite the predominance of very well-differentiated glands with minimal atypia in much of the tumor (see D, E), the deeper portion of the tumor (see C) contains infiltrative glands with more eosinophilic cytoplasm and atypical vesicular nuclei with prominent eosinophilic nucleoli.





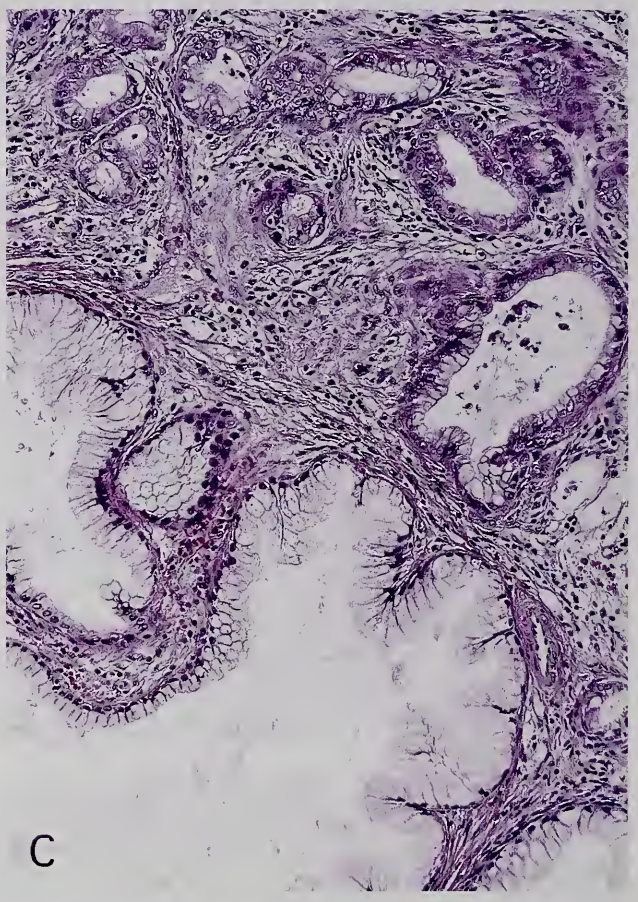


Figure 5-114

MINIMAL DEVIATION ADENOCARCINOMA, MUCINOUS TYPE

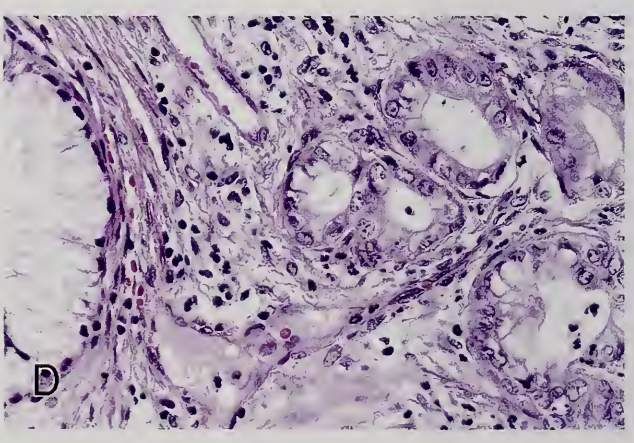
A: A diffuse glandular proliferation fills the cervical stroma and extends to the margins of the excisional specimen (figs. A thru E are from the same lesion).

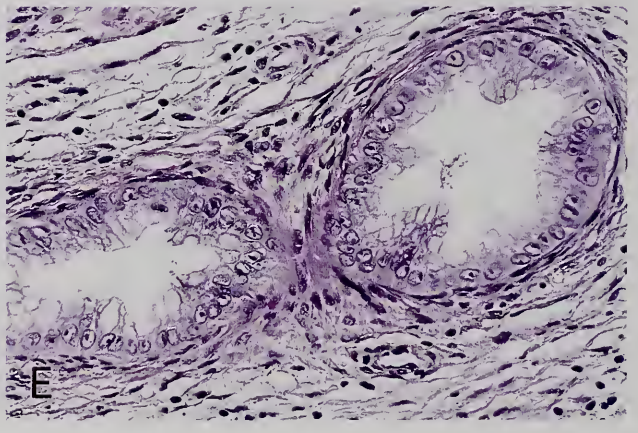
B: The proliferation in figure A contains both lobulated benign-appearing hypermucinous glands and smaller irregular infiltrative glands within a desmoplastic stroma. The deep location of the hypermucinous glands suggests they may be a very well-differentiated component of the neoplasm but their lobulated appearance suggests preexisting endocervical glandular hyperplasia.

C: Invasive, small, tightly clustered atypical glands within reactive stroma are distinct from adjacent larger hypermucinous glands, which may be a component of the neoplasm or preexisting glandular hyperplasia.

D: Small glands have distinctive nuclear atypia characterized by rounded vesicular nuclei with prominent nucleoli; an adjacent hypermucinous gland has small, basally situated, benign-appearing nuclei.

E: Deeply situated atypical glands exhibit distinctive nuclear atypia characterized by rounded vesicular nuclei with prominent nucleoli. They are surrounded by edematous desmoplastic stroma.





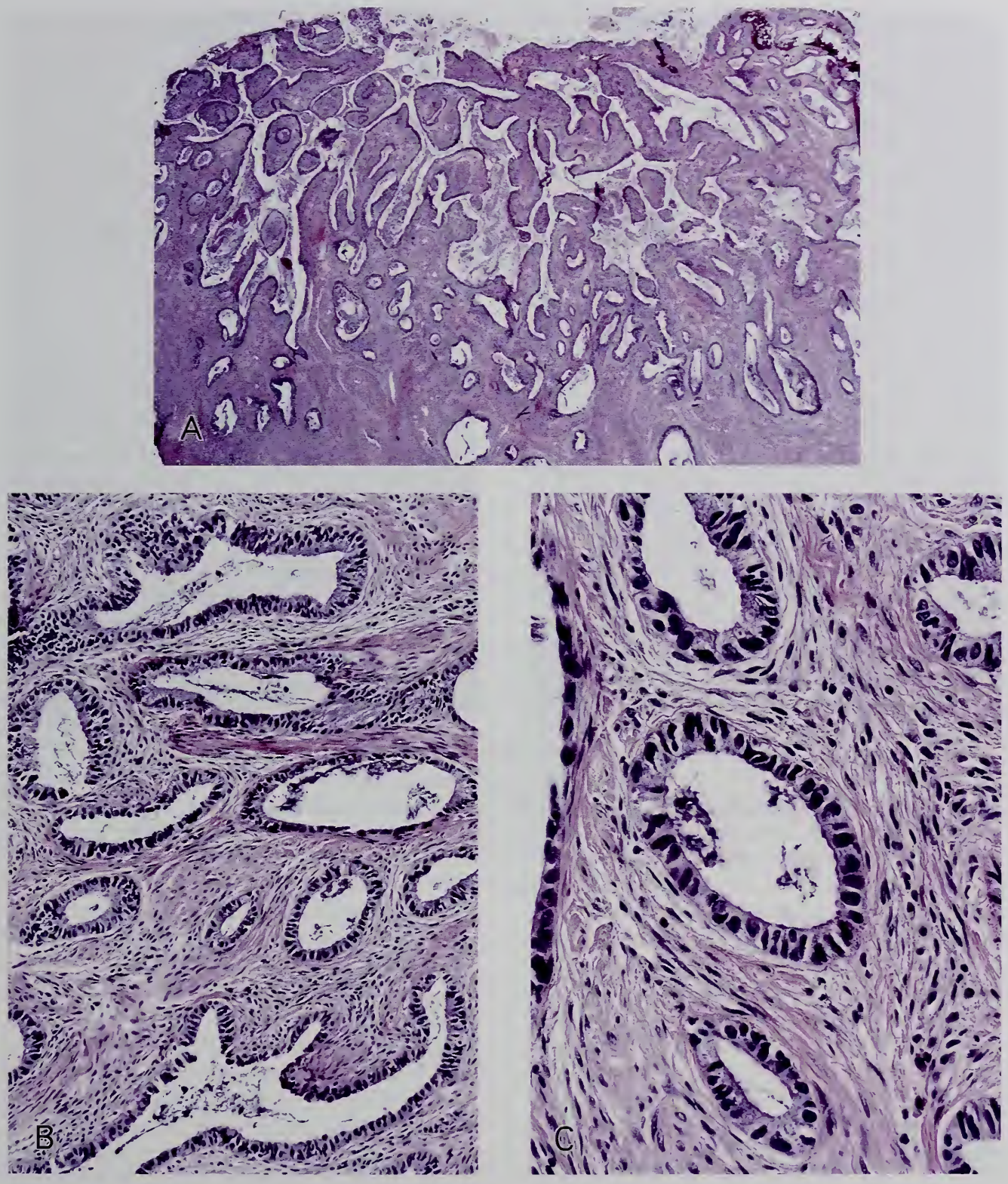


Figure 5-115

MINIMAL DEVIATION ADENOCARCINOMA, ENDOMETRIOID TYPE

A: A diffuse labyrinthine glandular proliferation extends deep into cervical stroma.

B: At higher magnification, well-differentiated endometrioid glands of variable size and shape, including one with a claw shape, are surrounded by desmoplastic stroma.

C: Well-differentiated endometrioid glands exhibit some nuclear atypia and are surrounded by desmoplastic stroma.

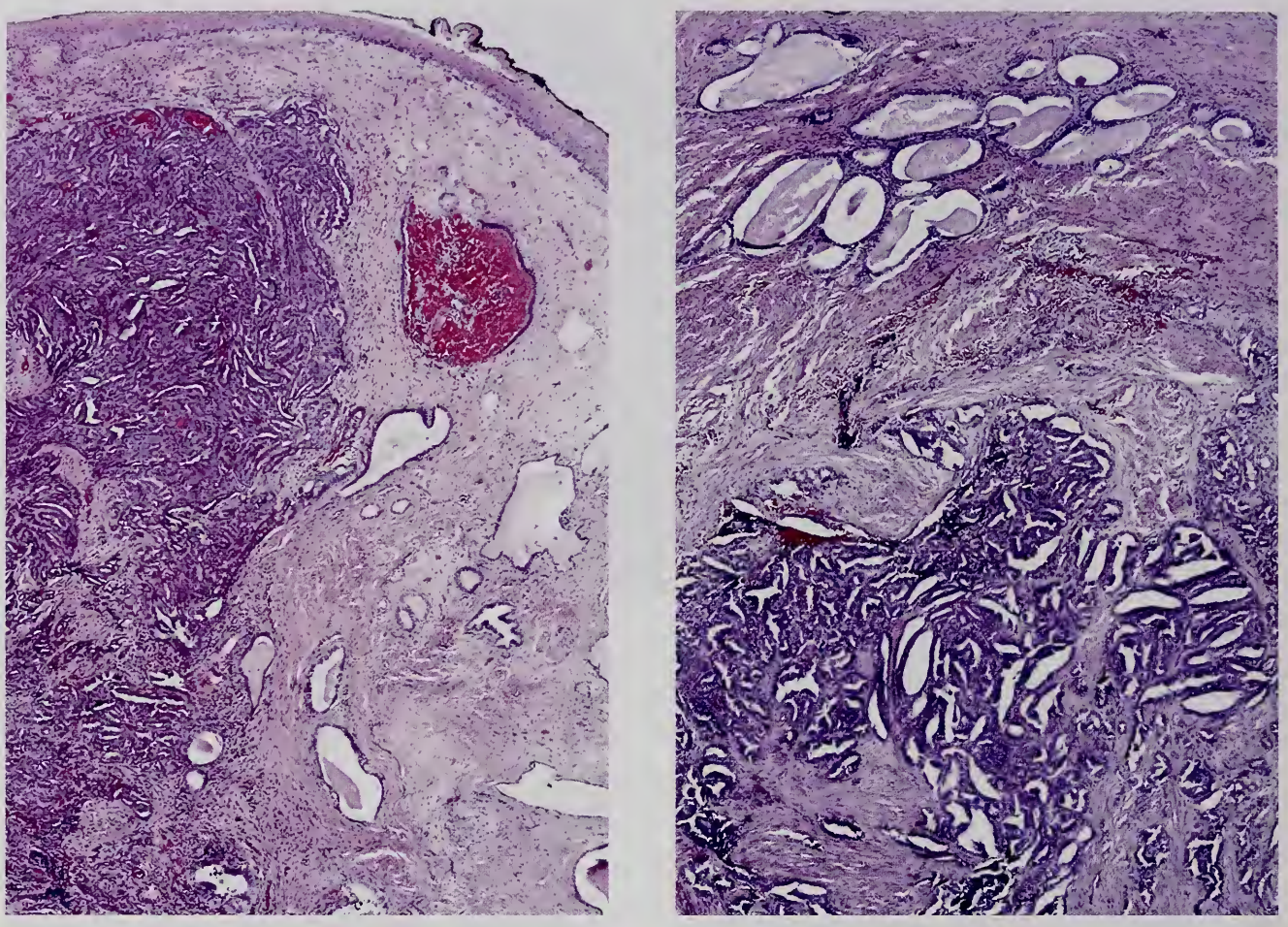


Figure 5-116

MESONEPHRIC ADENOCARCINOMA

Left: A densely crowded proliferation with a sieve-like confluent glandular pattern is present within the cervical stroma and merges with adjacent mesonephric remnants.

Right: Dilated mesonephric remnants are present adjacent to the adenocarcinoma.

mesonephric remnants tend to be deeply positioned, with the bulk of the tumor in the stroma forming tubules and glands. The tubules are usually closely packed and diffusely infiltrate the stroma in a haphazard arrangement (233). The cells lining the tubules are cuboidal or columnar and form a single layer. Most have darker, more granular cytoplasm than seen in clear cell carcinoma. The lumens generally contain eosinophilic, hyaline-like material (figs. 5-116, 5-117). On rare occasion, the tumor forms solid sheets, slit-like spaces, and papillary structures resembling serous carcinoma. In some cases a spindle cell component is present (379). A prominent basement membrane is often present about the periphery of the tubules as in benign remnants. Mesonephric carcinomas typically invade the wall of the cervix extensively but also usually extend close to the surface.

The major differential diagnosis is with mesonephric hyperplasia, particularly if cytologic atypia and mitotic activity are present. Mesonephric hyperplasia is generally not evident on gross examination whereas mesonephric carcinoma typically presents as a mass. Mesonephric hyperplasia generally maintains a vaguely lobular architecture and may be associated with a duct-like structure in contrast to mesonephric carcinoma which has an infiltrative pattern. The cells of mesonephric carcinoma have malignant-appearing nuclei and mitotic activity is increased, although these features are not present in all carcinomas (74). The tubular structures and glands in mesonephric hyperplasia are more

crowded and confluent than in hyperplasia and tend to have an associated stromal reaction.

Mesonephric carcinoma may be difficult to distinguish from the usual type of endocervical adenocarcinoma, particularly when the mesonephric carcinoma closely approaches and involves the superficial endocervical mucosa. Foci within mesonephric carcinoma can mimic endometrioid and serous carcinomas and the presence of a spindle cell component can suggest a carcinosarcoma (malignant mixed müllerian tumor [MMMT]). Mesonephric carcinoma can be distinguished from the usual type of endocervical carcinoma, as well as endometrioid and serous carcinomas, by its association with mesonephric remnants or hyperplasia, and the presence of the homogeneous eosinophilic material within the tubular lumens. Cervical carcinosarcomas, in contrast to mesonephric carcinomas with a spindle cell component, usually have a sharply demarcated, squamous or basaloid carcinomatous component apart from the spindle cell component. Clear cell carcinoma may superficially resemble mesonephric carcinoma but the latter lacks clear cells and hobnail cells and does not display the admixture of tubulocystic, papillary, and solid patterns that characterize clear cell carcinoma.

It has been reported that involvement of endocervical stroma by endometrial endometrioid carcinoma can simulate mesonephric carcinoma (396). Mesonephric carcinomas express CK7, EMA, CD10, and calretinin but not CK20, hormone receptors, or monoclonal CEA (261,304,305,374). Thus, immunohistochemistry for CD10, calretinin, and hormone receptors helps distinguish mesonephric carcinoma from endometrioid carcinoma in the cervix.

Most cases of mesonephric adenocarcinoma thus far reported have been confined to the cervix (stage IB) at presentation. Stage I tumors appear to have a more indolent behavior than the usual type of endocervical adenocarcinoma. A few advanced-stage tumors and those exhibiting a sarcomatoid pattern have behaved aggressively (74).

OTHER EPITHELIAL TUMORS

Adenosquamous Carcinoma

Definition. *Adenosquamous carcinoma* is a form of carcinoma exhibiting both glandular and squamous differentiation. It is commonly classified as a mixed carcinoma, a designation for a cervical carcinoma showing glandular and squamous differentiation, rather than listed within either the adenocarcinoma or squamous cell carcinoma category. In this text, adenosquamous carcinoma embraces any primary carcinoma containing malignant-appearing squamous and glandular elements. Thus, adenocarcinoma with bland squamous differentiation is not considered adenosquamous but rather endometrioid with squamous differentiation. Adenocarcinoma with bland squamous differentiation is rare as a primary carcinoma of the cervix. Typically, the squamous element is poorly differentiated and is the predominant component.

General Features. Adenosquamous carcinoma is 20 to 50 percent as common as adenocarcinoma of the cervix (329,371,398,403), depending on the microscopic criteria employed. Because of the variability in the definition, the clinical features are unsettled. Adenosquamous carcinoma is found in both old and young women, and is often reported in association with pregnancy. Notable differences in risk factor profiles for those with adenosquamous carcinoma and other cervical adenocarcinomas have been reported (52): multiple sexual partners, low education level, and an association with smoking suggest that the risk factors are more like those of squamous cell carcinoma of the cervix than those of adenocarcinoma. Also, compared to adenocarcinoma, adenosquamous carcinoma is more frequently poorly differentiated and more often demonstrates vascular invasion (421). Adenosquamous carcinoma is more aggressive than adenocarcinoma, and AIS is infrequently associated with adenosquamous carcinoma (421), making it less likely that screening for AIS or SIL will be effective in detecting adenosquamous carcinoma at an early stage.

Gross Findings. Adenosquamous carcinoma does not differ grossly from adenocarcinoma of the endocervix, appearing as an ulcerated nodular or polypoid firm mass.

Microscopic Findings. The glandular component is usually poorly differentiated, and shows some degree of mucinous differentiation in the form of minor cytoplasmic vacuolization and accumulation of mucin in gland lumens. The squamous component is poorly differentiated,

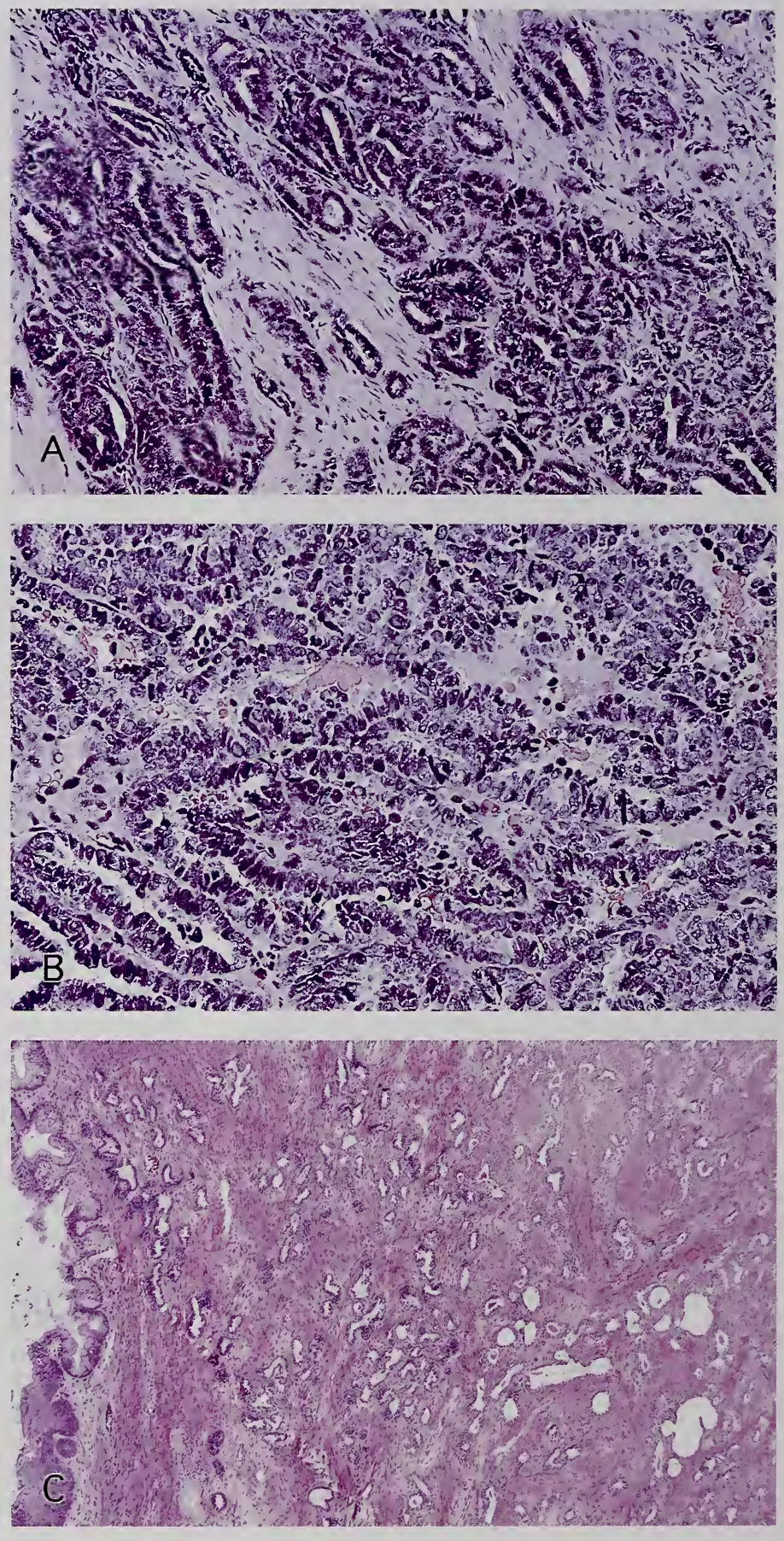


Figure 5-117

MESONEPHRIC ADENOCARCINOMA

A: Small tubular glands have an endometrioid appearance and infiltrate the fibrous stroma.

B: Crowded glands are composed of columnar cells with hyperchromatic nuclei and scant cytoplasm; mitotic figures are evident.

C: A diffuse proliferation of small tubular glands extends throughout the cervical stroma.

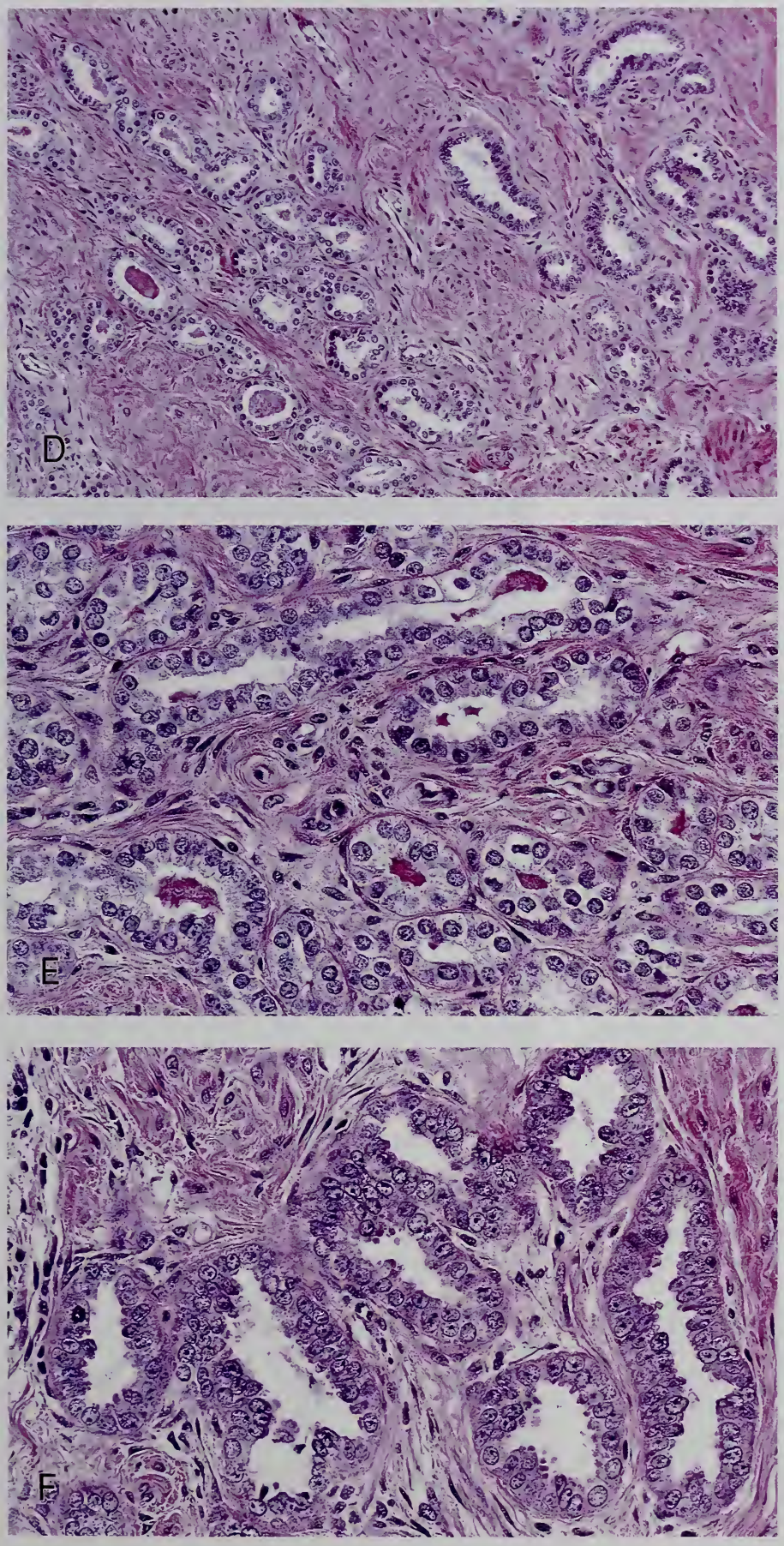


Figure 5-117 (Continued)

D: Small tubular glands lined by cuboidal epithelium contain characteristic dense eosinophilic secretions.

E: Tubular glands are lined by cells with round enlarged nuclei having granular chromatin; occasional nucleoli are evident.

F: Atypical glands have enlarged vesicular nuclei with prominent nucleoli. One mitotic figure is evident.

showing little keratinization (fig. 5-118). The glandular component can be graded architecturally, as for adenocarcinoma, and by nuclear grade of the glandular and squamous components. Some adenosquamous carcinomas resemble the mucoepidermoid carcinoma seen in the head and neck, and some have used the term "mucoepidermoid carcinoma" to describe them. Most authorities, however, have not adopted this terminology for cervical neoplasms.

Differential Diagnosis. Extension of a primary, poorly differentiated adenocarcinoma of the endometrium with squamous differentiation into the endocervix and primary endocervical adenocarcinoma coexisting with HSIL or squamous cell carcinoma as a collision tumor must be excluded. In cases of poorly differentiated adenocarcinoma with squamous differentiation of the endometrium extending to the cervix, the bulk of the tumor is in the endometrium and thus there is usually less clinical involvement of the cervix by a stage II endometrial carcinoma than by a stage I cervical carcinoma. In cases in which the neoplasm involves the corpus and cervix to an equal extent, it may be impossible to define the primary site, even after hysterectomy. An adenocarcinoma coexisting with HSIL or pure squamous carcinoma as a collision tumor lacks the intermingling of the two elements that is seen in cases of adenosquamous carcinoma.

Treatment and Prognosis. The treatment for adenosquamous carcinoma is the same as that for other forms of carcinoma of the cervix. The survival rate of patients vary from no different than that of patients with squamous cell carcinoma or adenocarcinoma (223,329,371) to a much worse prognosis (118,124,348,421). In reports where the diagnosis is limited to neoplasms in which both glandular and squamous components appear malignant, the prognosis is poor. Reported series are small and microscopic criteria vary, leading to inconsistent conclusions.

Glassy Cell Adenocarcinoma

Definition. *Glassy cell adenocarcinoma* is a poorly differentiated carcinoma characterized by sheets of cells having a moderate amount of cytoplasm with a ground-glass or granular appearance, a distinct cytoplasmic membrane, and a large nucleus containing prominent single or multiple nucleoli.

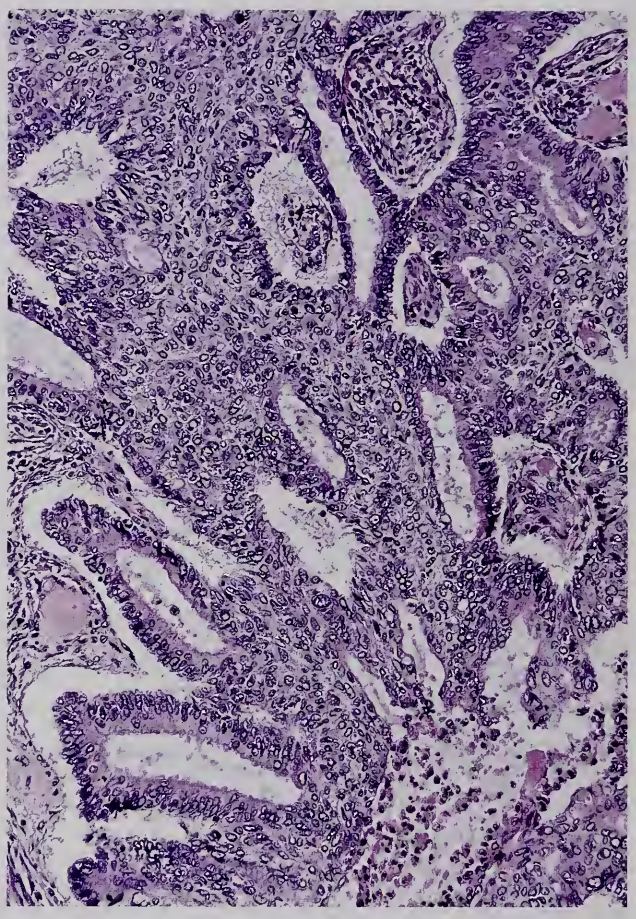


Figure 5-118

ADENOSQUAMOUS CARCINOMA

Glandular epithelium merges with solid epithelium exhibiting squamous differentiation.

General Features. Glassy cell carcinoma accounts for only 1 to 2 percent of all cervical carcinomas (61,244,250), but as much as 10 percent of adenocarcinomas (118,360). It was originally classified within the group of mixed (adenosquamous) carcinomas (61). It occurs in younger patients (mean age, 31 to 41 years) compared to those with squamous cell carcinoma or ordinary adenocarcinoma of the cervix, and was associated with pregnancy in an unexpected number of cases in early reports, but not in more recent series. HPV 18 has been detected in two of three cases that were analyzed by PCR (204).

Gross Findings. Glassy cell carcinoma appears as a bulky exophytic mass. Despite this presentation, the invasion is characteristically less deep than suspected from the size of the protuberant mass (397).

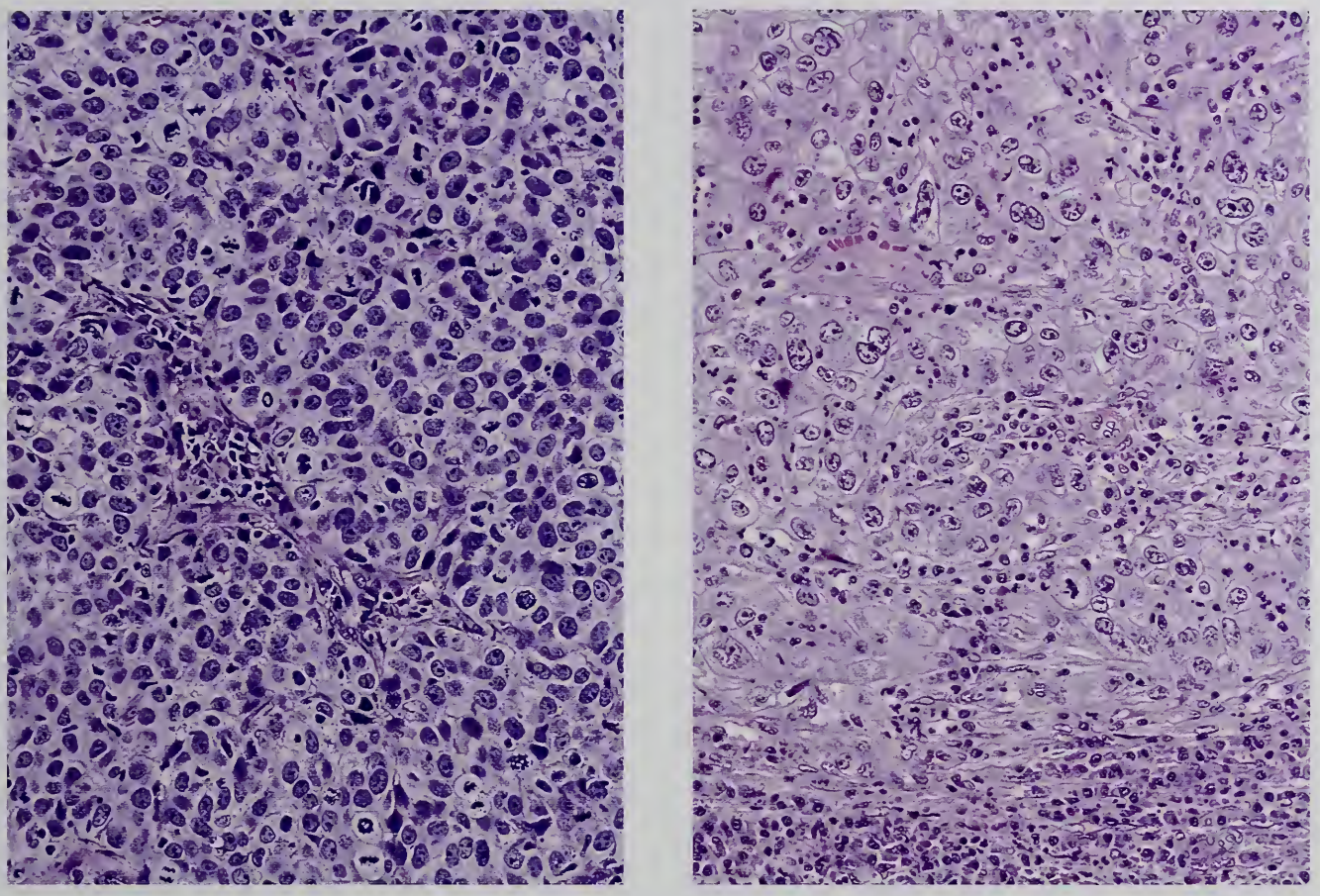


Figure 5-119

GLASSY CELL CARCINOMA

Left: Solid sheets of tumor are composed of cells with distinct cell borders, abundant clear to granular eosinophilic cytoplasm, and large atypical nuclei with prominent nucleoli.

Right: Tumor cells have distinct cell borders, abundant granular eosinophilic cytoplasm, and large atypical vesicular nuclei with prominent nucleoli, and are associated with a chronic inflammatory cell infiltrate.

Microscopic Findings. The tumor is composed of invasive nests and sheets of cells, often separated by delicate fibrovascular septa. The neoplastic cells are uniform, large, and polygonal, with a distinct cell border. The cells contain large oval nuclei, prominent nucleoli, and moderate amounts of finely granular, pale eosinophilic or amphophilic cytoplasm resembling ground glass. Mitotic figures are numerous. Minor degrees of keratinization, infrequent intercellular bridges, rare gland lumens, and intracellular mucin positivity may occur (250). An intense inflammatory infiltrate is present in the stroma, usually containing numerous eosinophils and plasma cells (fig. 5-119) (244). Areas of glassy cell carcinoma are often admixed in what are otherwise high-grade cervical carcinomas; pure glassy cell carcinomas are uncommon.

Cytologic Findings. Cervical smears reveal scattered clusters of cells and single cells with large nuclei, prominent single or multiple nucleoli, and a moderate amount of finely granular cytoplasm in a background of inflammatory cells and proteinaceous debris (299). Cytoplasmic membranes are distinct, and mitotic figures are common. Distinction must be made from reactive atypia, which does not occur in isolated cells, and nonkeratinizing squamous cell carcinoma cells (309), which show more nuclear irregularity and an indefinite cytoplasmic margin.

Differential Diagnosis. The main entity in the differential diagnosis is poorly differentiated nonkeratinizing squamous cell carcinoma. The latter is composed of cells similar in size to glassy cells but with more oval nuclei, syncytial growth of the cells, and fewer mitotic figures

than glassy cell carcinoma. The chromatin of the cells of nonkeratinizing squamous cell carcinoma is coarser and distributed along the nuclear membrane. The cytoplasm is less finely granular, and the cytoplasmic membrane is less well defined (212). Poor fixation and pale staining of paraffin sections tends to obscure the features of nonkeratinizing squamous cell carcinoma to the degree that it may resemble glassy cell carcinoma. Not all investigators have found cytologically distinctive features in glassy cell carcinoma. It may be that glassy cell carcinoma is a form of poorly differentiated nonkeratinizing squamous cell or adenosquamous carcinoma.

Treatment and Prognosis. Therapy is the same as for invasive squamous cell carcinoma and adenocarcinoma of the same stage, but the prognosis is not as good. In a study of 29 patients with stage IB glassy cell carcinomas, the survival rate was only 55 percent, about 20 percent lower than that for squamous cell carcinoma (309,397). The reputation of a poor prognosis, however, is based on only a few cases in each stage, so it can be questioned whether glassy cell carcinoma is worse than any other poorly differentiated carcinoma of the cervix (250). Part of the difficulty in assessing the results of therapy and relating it to prognosis is due to the variable microscopic criteria applied in the past and a degree of subjectivity in making the diagnosis.

Adenoid Cystic Carcinoma

Definition. *Adenoid cystic carcinoma* of the cervix resembles adenoid cystic carcinoma of the salivary gland.

General Features. Adenoid cystic carcinoma of the cervix is a rare tumor, representing less than 1 percent of cervical adenocarcinomas (283). Most of the reported 120 examples are single case reports or small series of cases (212). In early reports, adenoid cystic carcinoma was confused with adenoid basal cell carcinoma because of overlapping pathologic features. The two neoplasms are distinct both clinically and pathologically and should be designated separately. Adenoid cystic carcinoma has been shown to contain high-risk HPV DNA and thus is another HPV-related type of cervical carcinoma (141,313).

Clinical Features. Patients with adenoid cystic carcinoma tend to be elderly, with few under 50 years of age (169,275). Reports from the United States contain a higher proportion of African-Americans than anticipated from the general population (109,283,412). The parity of patients with adenoid cystic carcinoma and the stage of tumor at its discovery are the same as for adenocarcinoma of the cervix. Ovarian epithelial tumors, particularly mucinous ones, are common in women with adenoid cystic carcinoma.

Gross Findings. Adenoid cystic carcinomas usually form hard, irregular, polypoid friable masses, although some are endophytic and ulcerated.

Microscopic Findings. The cells form clusters, cords, and trabeculae with a circular or spiral pattern (fig. 5-120). Hyaline eosinophilic material is present within gland lumens. The nuclei are small, dark, and uniform, and seldom show pleomorphism. Minor areas of squamous differentiation may be present. Mitotic figures and necrosis are common, and hyalinization of the stroma may be prominent. The microscopic patterns overlap with those of ordinary adenocarcinoma and adenoid basal carcinoma (109,275,324). Unlike adenoid cystic carcinoma of the salivary gland, adenoid cystic carcinoma of the cervix lacks myoepithelial cells and a propensity for perineural invasion. Because ordinary forms of adenocarcinoma are mixed with adenoid cystic carcinoma and myoepithelial differentiation is lacking, investigators have proposed that most adenoid cystic carcinomas of the cervix are adenocarcinomas with adenoid cystic differentiation (109). Lymphatic invasion is usually evident (275).

A solid variant of adenoid cystic carcinoma has been reported (12). The stroma typically contains abundant PAS-positive basement membrane material that is immunoreactive for collagen IV. This is a distinctive feature of the tumor and appears to be the best marker for its identification. As with the more common cystic variant, there is an absence of neurosecretory granules and myoepithelial cells.

Immunohistochemical Findings. Immunostains for cytokeratins are usually strongly positive, whereas CEA and EMA staining is focal. Actin and S-100 protein stains for myoepithelial cells are negative in most adenoid cystic carcinomas of the cervix, unlike adenoid cystic carcinomas in other locations.

Differential Diagnosis. The main entities in differential diagnosis are adenoid basal cell carcinoma and small cell carcinoma. Adenoid basal cell carcinoma contains basaloid cells with peripheral palisading and often has squamous and glandular differentiation, but the glands lack the globules of basement membrane material found in adenoid cystic carcinoma. Small cell carcinoma also lacks abundant basement membrane material and gland formation.

Treatment and Prognosis. Adenoid cystic carcinoma of the cervix is aggressive. Similar to adenoid cystic carcinoma of the salivary glands, cervical adenoid cystic carcinoma frequently metastasizes to distant visceral organs without involving regional lymph nodes. In one study, 5 of 12 patients died of tumor or had local recurrence along with distant metastasis to lung, liver, bone, or other sites (275). In other studies, the behavior was similar to, or worse than, adenocarcinoma and squamous cell carcinoma of the cervix (109,212,412).

Adenoid Basal Cell Tumors

Definition. *Adenoid basal cell tumors* are characterized by nests and cords of small oval cells with a peripheral palisaded arrangement, resembling basal cell and basosquamous cell carcinomas of the skin. They include low-grade appearing tumors (epitheliomas) and histologically malignant-appearing tumors (carcinomas) having adenoid basal differentiation, with or without the other types of differentiation seen in invasive cervical carcinomas.

General Features. An uncommon neoplasm, *adenoid basal cell carcinoma* was first identified as an entity distinct from adenoid cystic carcinoma in 1966 (26). Since then, additional cases have been reported (26,92,109,412). It justifies a separate designation because it tends to occur in elderly women, and in all instances, was discovered while confined to the cervix. Metastasis is not reported in patients whose tumors have the typical microscopic pattern. Because of this lack of aggressive behavior, some have proposed that the neoplasm be termed *adenoid basal cell epithelioma* (49). Nonetheless, it is generally regarded as a carcinoma because of its infiltrative growth pattern and its extension to the lower uterine segment in some instances. Recently, it has been proposed that adenoid basal tumors be divided into benign and malignant types based on morphologic features (see below) (313).

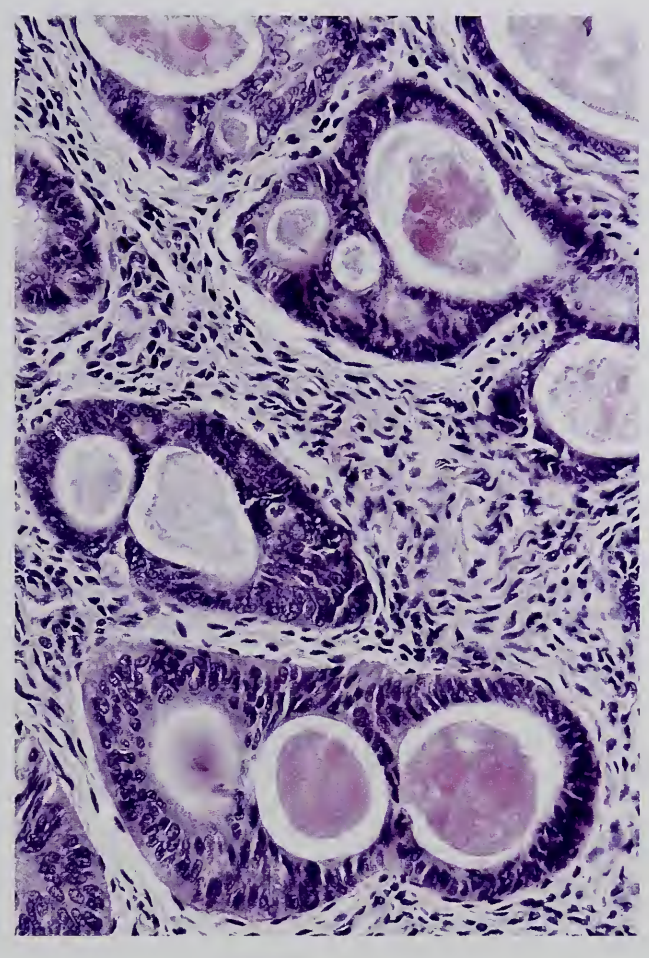


Figure 5-120

ADENOID CYSTIC CARCINOMA

Cribriform glands are lined by columnar basaloid cells. Dense eosinophilic material is present in the lumens.

Several studies have shown that these tumors contain both integrated and episomal high-risk HPV (inferred by distribution of the positive signal by in situ hybridization studies), usually type 16 and less commonly type 33 (142,189). Furthermore, in studies in which adenoid basal epitheliomas and carcinomas were associated with adjacent invasive carcinomas of other types, HPV was detected in the adenoid basal epithelioma, adenoid basal carcinoma, and other types of carcinomas, suggesting that adenoid basal tumors arise from a reserve cell with the potential for differentiating along different pathways (142,144,313).

Clinical Features. Patients tend to be older than most with adenocarcinoma, with a median

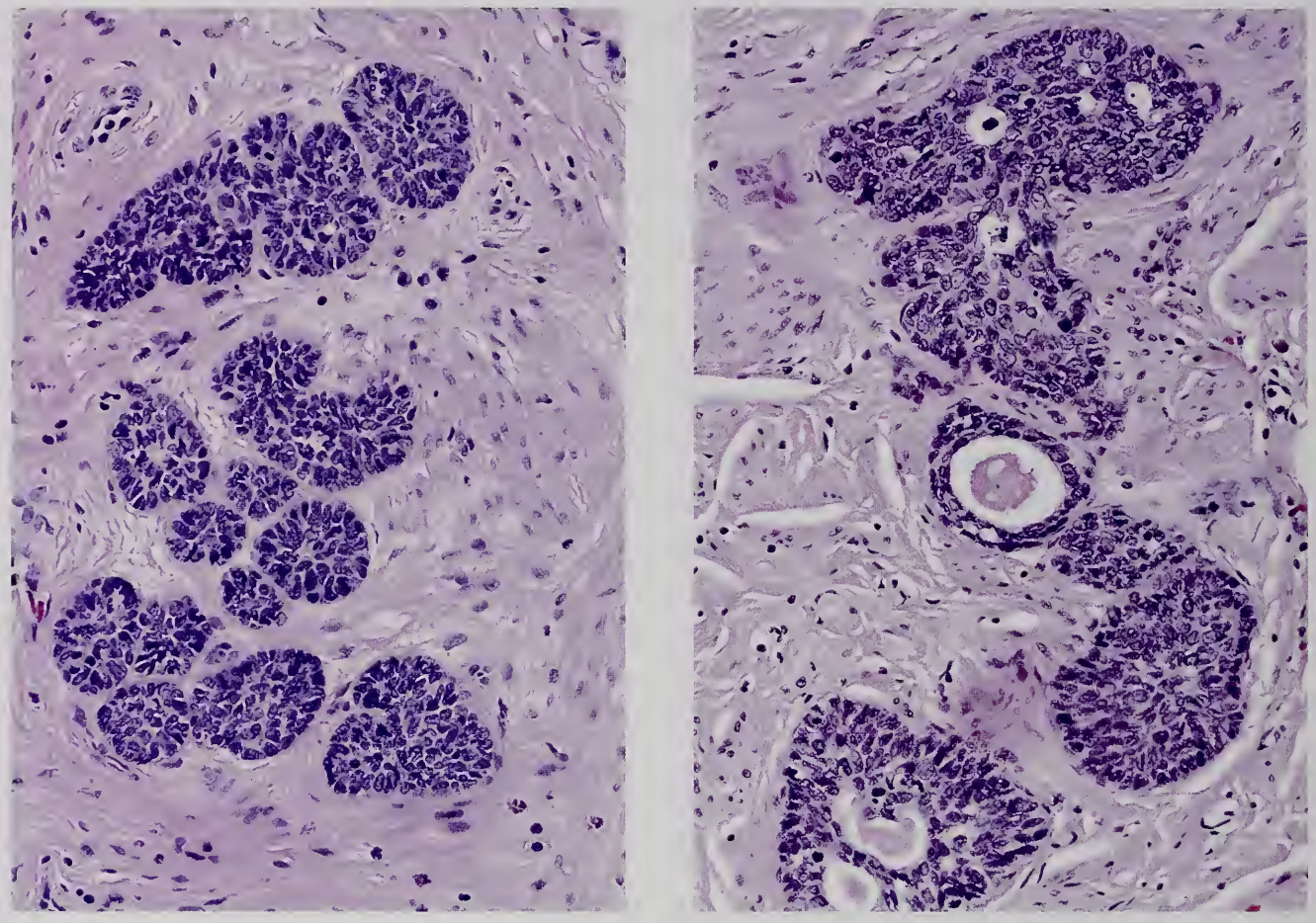


Figure 5-121

ADENOID BASAL CELL TUMOR (EPITHELIOMA)

Left: Basaloid solid epithelial nests are surrounded by nonreactive fibrous stroma.
Right: Basaloid epithelial nests have central glandular differentiation.

age of about 60 years. Nearly half of the patients are African-Americans. Adenoid basal tumors clinically differ markedly from ordinary adenocarcinoma of the cervix mainly by their early presentation (stage IA or IB) and lack of symptoms related to the lesion. Cytology smears are atypical or only suspicious in most cases and are related to an associated or overlying SIL, which is usually high grade. In most cases, the tumor is incidentally discovered in a uterus removed for definitive treatment of a HSIL.

Gross Findings. The cervix appears normal or shows a mild nodular distortion.

Microscopic Findings. Adenoid basal cell tumors of the low-grade variety (adenoid basal epithelioma) (49,313) resemble basal cell carcinoma of the skin with squamous differentiation. Small nests and cords of uniform round cells or oval small cells with scant cytoplasm and small dark nuclei characterize the tumor (figs. 5-121, 5-122). Squamous differentiation occurs centrally, with the squamous cells surrounded or capped by smaller rounded basal cells. A few of the cords or nests contain small acini lined by a single layer of cuboidal to columnar cells; mitotic figures are infrequent. A desmoplastic stromal reaction is generally absent. Most tumors are located at the lower level of endocervical glands or deeper, and involvement of the overlying surface is minimal or absent. An accompanying HSIL is often present and on occasion the tumor is connected to the overlying epithelium involved by the HSIL.

Adenoid basal cell tumors having malignant cytologic features are classified as carcinomas (fig. 5-123) (140,313). They can exhibit pure

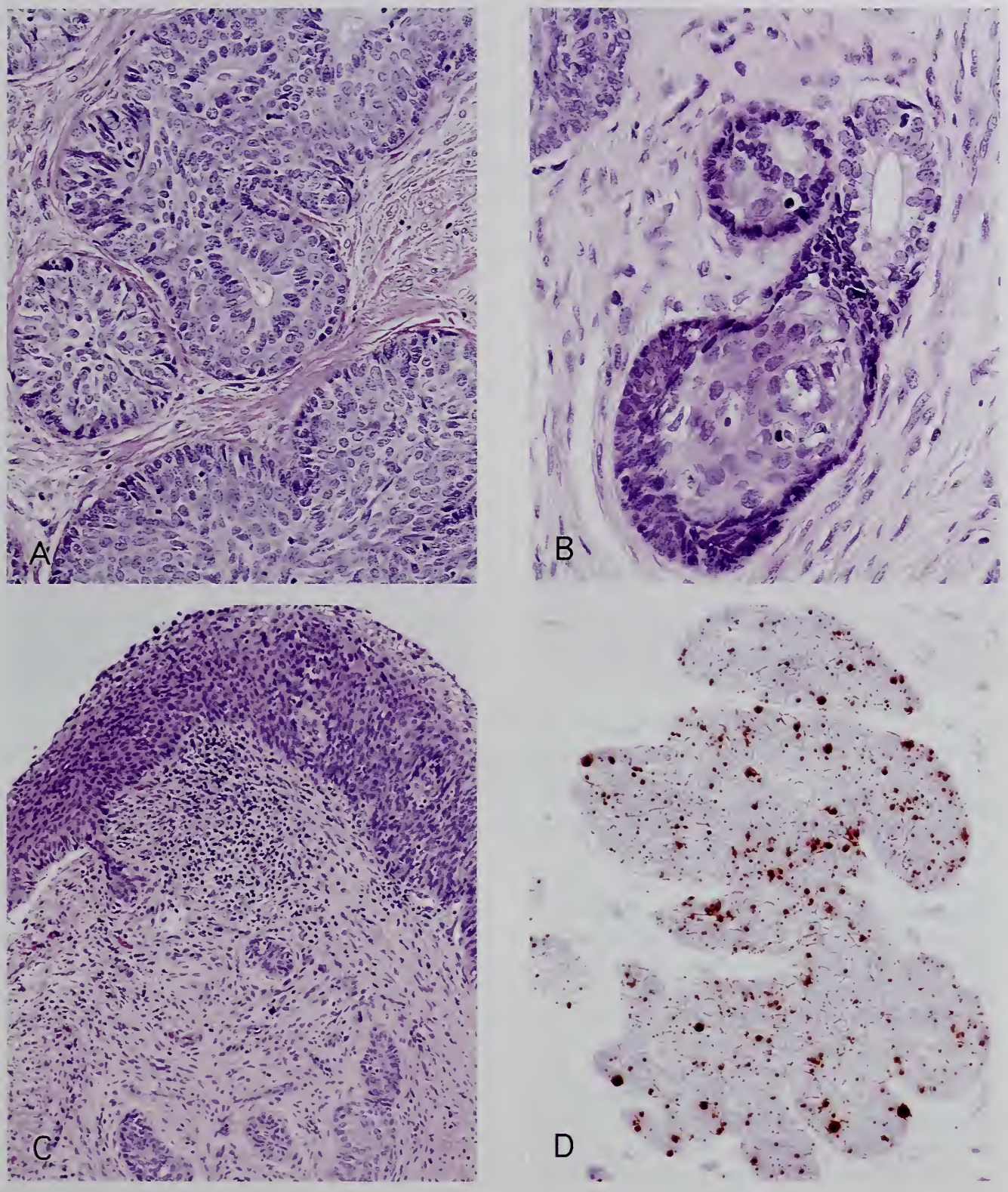


Figure 5-122

ADENOID BASAL CELL TUMOR (EPITHELIOMA)

A: Basaloid epithelial nests exhibit peripheral palisading and central glandular differentiation.
B: Epithelial nests have peripheral basaloid and central squamous and glandular differentiation.
C: A small nest is budding from the overlying HSIL.
D: In situ hybridization for HPV 16 demonstrates the punctate nuclear signals that indicate a positive result.

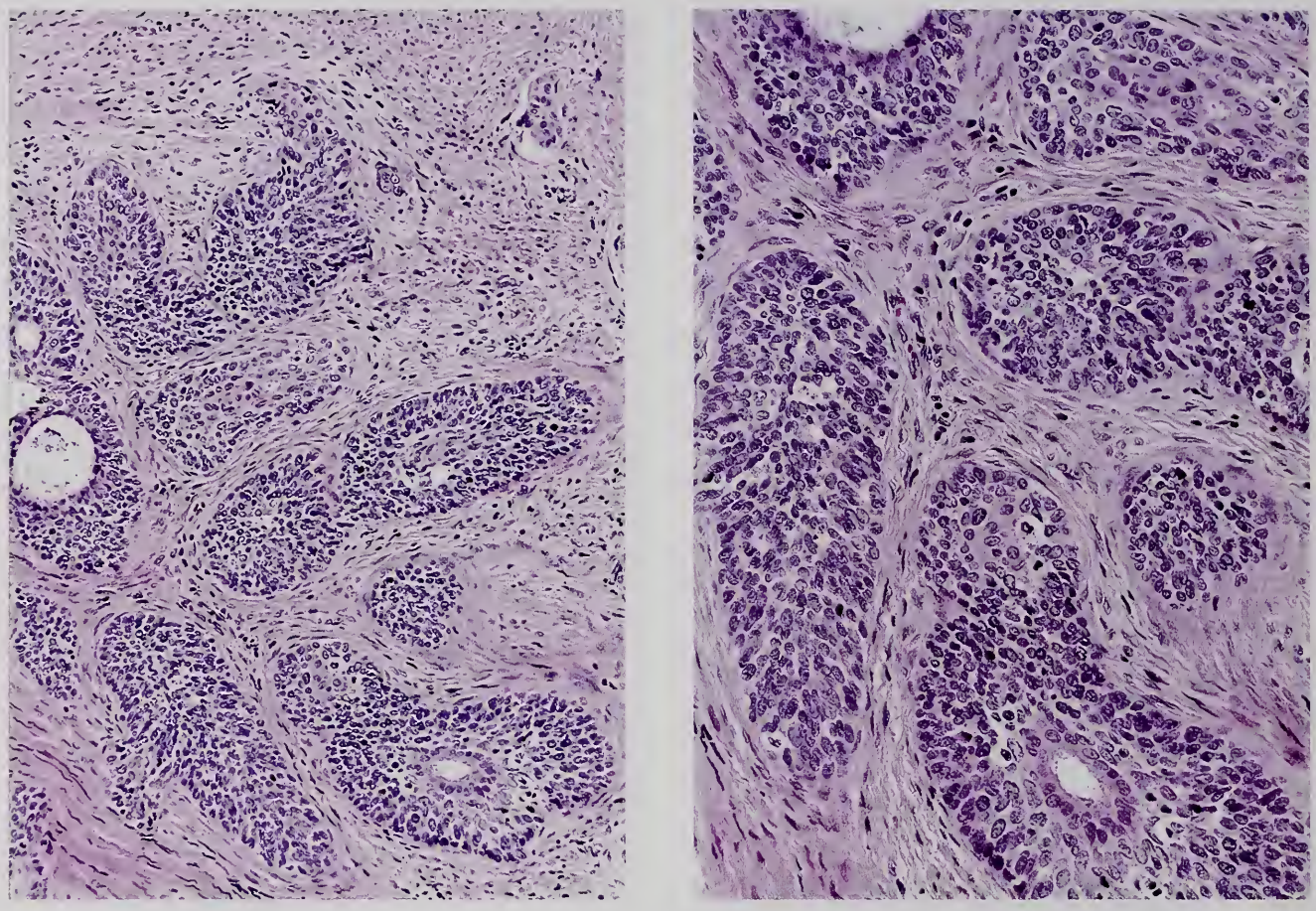


Figure 5-123

ADENOID BASAL CELL CARCINOMA

Left: Nests of basaloid tumor cells with central glandular differentiation are deep within the cervical stroma. A small nest of tumor is present within a lymphatic space.

Right: Basaloid tumor cells have atypical hyperchromatic nuclei with granular chromatin. Mitotic activity is evident.

adenoid basal type differentiation or be accompanied by carcinomatous components displaying other forms of differentiation encountered in cervical carcinomas, including squamous and adenoid cystic (figs. 5-124, 5-125).

Differential Diagnosis. Adenoid basal cell tumors should be distinguished from pseudoepitheliomatous hyperplasia associated with inflammation. In pseudoepitheliomatous hyperplasia and acanthosis from healing erosions, nests of epithelial cells appear disconnected from the surface. Squamous metaplasia can fill the superficial glands, producing bland nests resembling adenoid basal epithelioma. Adenoid basal tumors, however, forms nests and cords oriented haphazardly below the deepest level of endocervical glands. Furthermore, adenoid basal tumors involve the surface minimally or not at all, and are seldom associated with a significant degree of inflammation.

Adenoid basal cell tumors should be distinguished from adenoid cystic carcinoma and pure basaloid squamous carcinoma. Adenoid cystic carcinoma is more glandular, forming cystic spaces that contain pale, eosinophilic, basement membrane-like material. Adenoid cystic carcinoma is larger, involves the surface more extensively, is more widely infiltrative, and lacks squamous nests. Pure basaloid squamous cell carcinoma lacks an associated adenoid basal epithelioma component.

Treatment and Prognosis. Malignant behavior has not been observed for either adenoid basal epitheliomas or adenoid basal carcinomas (26,27,49,89,142,143,189,313,412), with the rare exception of one unusual case (109). Most

tumors are incidental findings in conization or hysterectomy specimens performed for treatment of HSIL. Conization may suffice as treatment for adenoid basal epithelioma when the margins are negative and an invasive carcinomatous component is not identified. Hysterectomy has usually been performed for most cases because the tumors tend to be deeply located and is recommended when a carcinomatous component is present.

NEUROENDOCRINE TUMORS

Tumors displaying neuroendocrine differentiation are rare in the cervix and their terminology has been confusing. Cases have been reported under the designation of *carcinoid, endocrine carcinoma, adenocarcinoma with endocrine granules, argyrophil cell carcinoma*, and *neuroendocrine carcinoma*, reflecting their diverse morphology and relationship to adenocarcinoma and small cell undifferentiated carcinoma. A consensus workshop sponsored by the College of American Pathologists and the National Cancer Institute proposed terminology similar to that used in the lung (10). In this classification, *neuroendocrine tumors* of the cervix are classified as *typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma*, and *small cell carcinoma*.

The following polypeptides have been identified in cervical carcinoid tumors: somatostatin, calcitonin (408), vasoactive intestinal polypeptide, antidiuretic hormone (ADH), pancreatic polypeptide, melanocyte stimulating hormone, adrenocorticotropic hormone (ACTH), glucagon, insulin, gastrin (431), serotonin, and histamine (173,257,373). Some neoplasms produce as many as five immunoreactive substances (257).

Paraendocrine syndromes from cervical neoplasms are rare and include Cushing syndrome (245,257), carcinoid syndrome, and hypoglycemia. These are more likely to stem from small cell carcinoma than from a true carcinoid tumor of the cervix. Neuroendocrine tumors of the cervix resemble those in other sites and the reader is directed to the Fourth Series Fascicles *Tumors of the Adrenal Glands and Extraadrenal Paraganglia* (232a), *Tumors of the Pancreas* (170a) and the Third Series Fascicle *Tumors of the Intestines* (333a), regarding the general morphologic, immunohistochemical, and ultrastructural features of these entities.

Typical Carcinoid Tumor

Among the neuroendocrine tumors involving the cervix, the *typical carcinoid tumor* is the least common. Typical carcinoids are small and well circumscribed. The tumor cells grow in sheets, nests, and cords, separated by a fibrous stroma and are polygonal, columnar, or rarely, spindled. Nuclei are uniform and round or oval and have coarse stippled chromatin. Mitotic figures number less than 2 per 10 high-power fields. Although the diagnosis of carcinoid and other neuroendocrine tumors is confirmed with argyrophil stains or electron microscopy to identify dense core neurosecretory granules, we rely on immunohistochemical staining for neuron-specific enolase, chromogranin, synaptophysin, and CD56 to confirm the diagnosis.

Too few carcinoid tumors of the cervix have been reported to precisely delineate their behavior. Limited experience suggests that they have low malignant potential, similar to carcinoids of the gastrointestinal tract and lung.

Atypical Carcinoid Tumor

Atypical carcinoid tumors are the most common cervical carcinoid tumors. They resemble typical carcinoid tumors microscopically but have greater nuclear atypia. They are distinguished from typical carcinoids by the presence of a higher mitotic index (2 to 10 mitotic figures per 10 high-power fields) and the presence of coagulative tumor cell necrosis. As with typical carcinoid tumors of the cervix, limited reported experience precludes defining their clinical behavior. They appear to be somewhat more aggressive than typical carcinoids (252).

Small Cell Carcinoma

Definition. *Small cell carcinoma* is composed of a uniform population of small cells with a high nuclear-cytoplasm ratio, resembling small cell carcinoma (oat cell carcinoma) of the lung.

General Features. Small cell carcinoma represents 2 to 5 percent of all cervical carcinomas. Patients are the same age or younger than those with ordinary forms of invasive cervical carcinoma. Noted for its aggressive behavior (146, 316,414,416), small cell carcinoma is

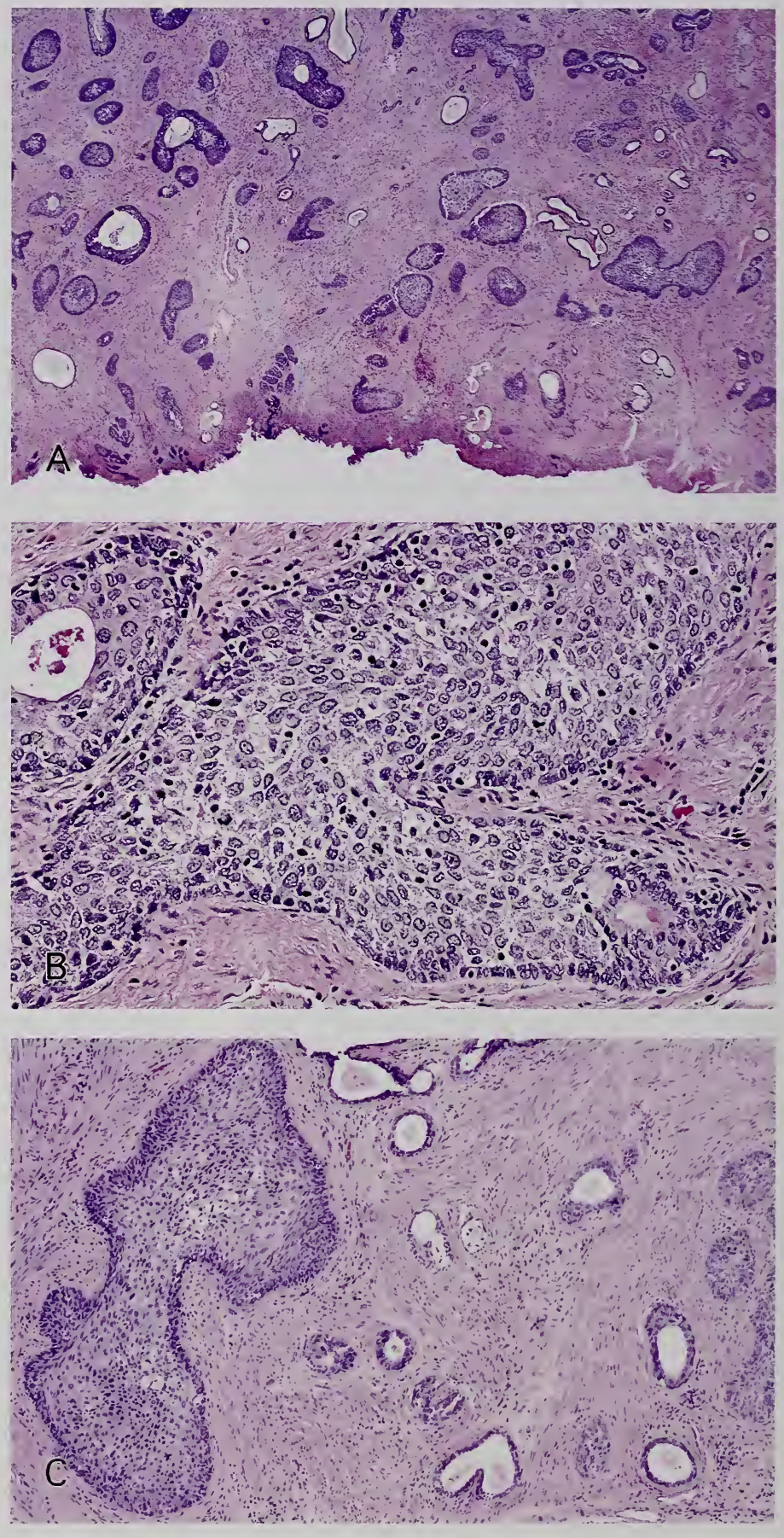


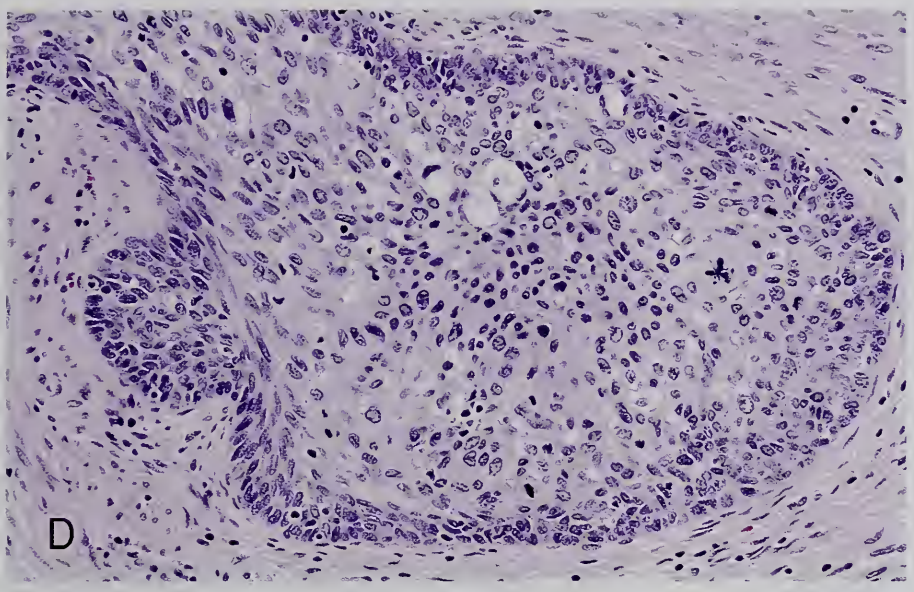
Figure 5-124

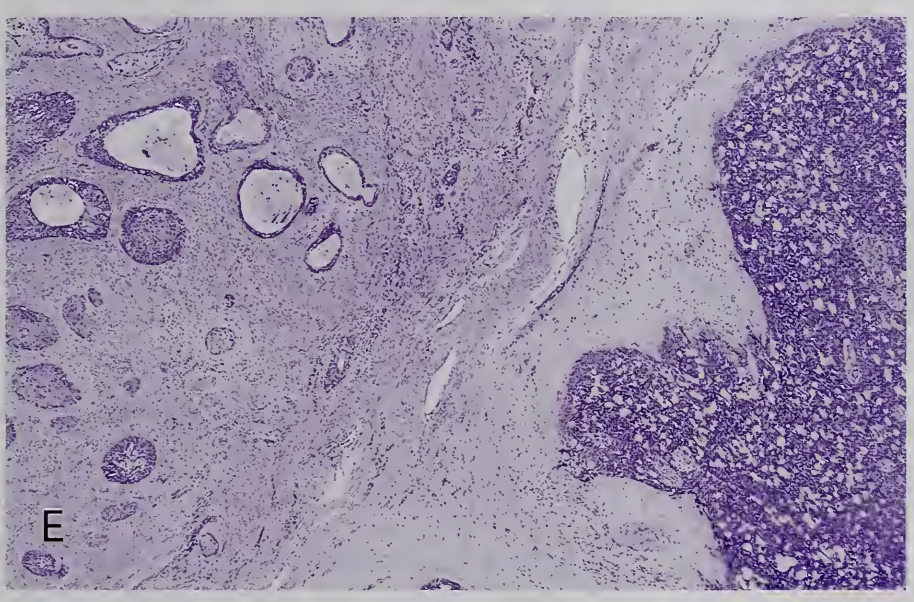
ADENOID BASAL CELL TUMOR: EPITHELIOMA WITH SQUAMOUS CELL CARCINOMA AND ADENOID CYSTIC CARCINOMA

A: Nests of tumor cells diffusely infiltrate the cervical stroma and extend to the margin of the specimen.

B: At higher magnification, solid nests of tumor cells exhibiting more obvious squamous differentiation, with nuclear atypia and mitotic activity, are consistent with carcinoma.

C: A large nest of squamous cell carcinoma is adjacent to smaller nests of adenoid basal epithelioma displaying varying degrees of basaloid and glandular differentiation.





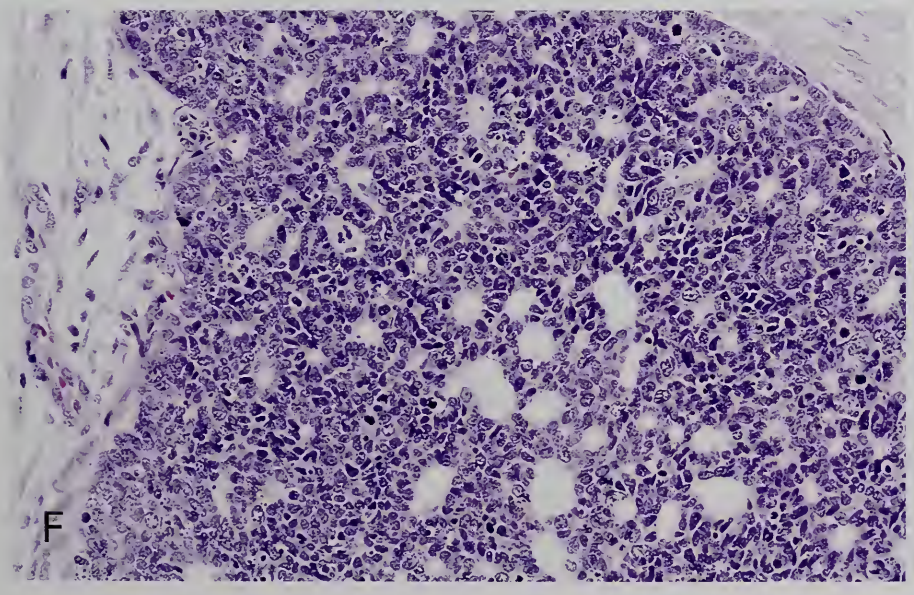


Figure 5-124 (Continued)

D: At higher magnification, an epithelial nest with peripheral basaloid and central squamous differentiation, nuclear atypia, and an atypical mitotic figure is consistent with squamous carcinoma.

E: Small nests of low-grade adenoid basal tumor are adjacent to a large island of adenoid cystic carcinoma (solid variant).

F: At higher magnification, the solid variant is composed of atypical basaloid cells with numerous mitotic figures and apoptotic bodies.

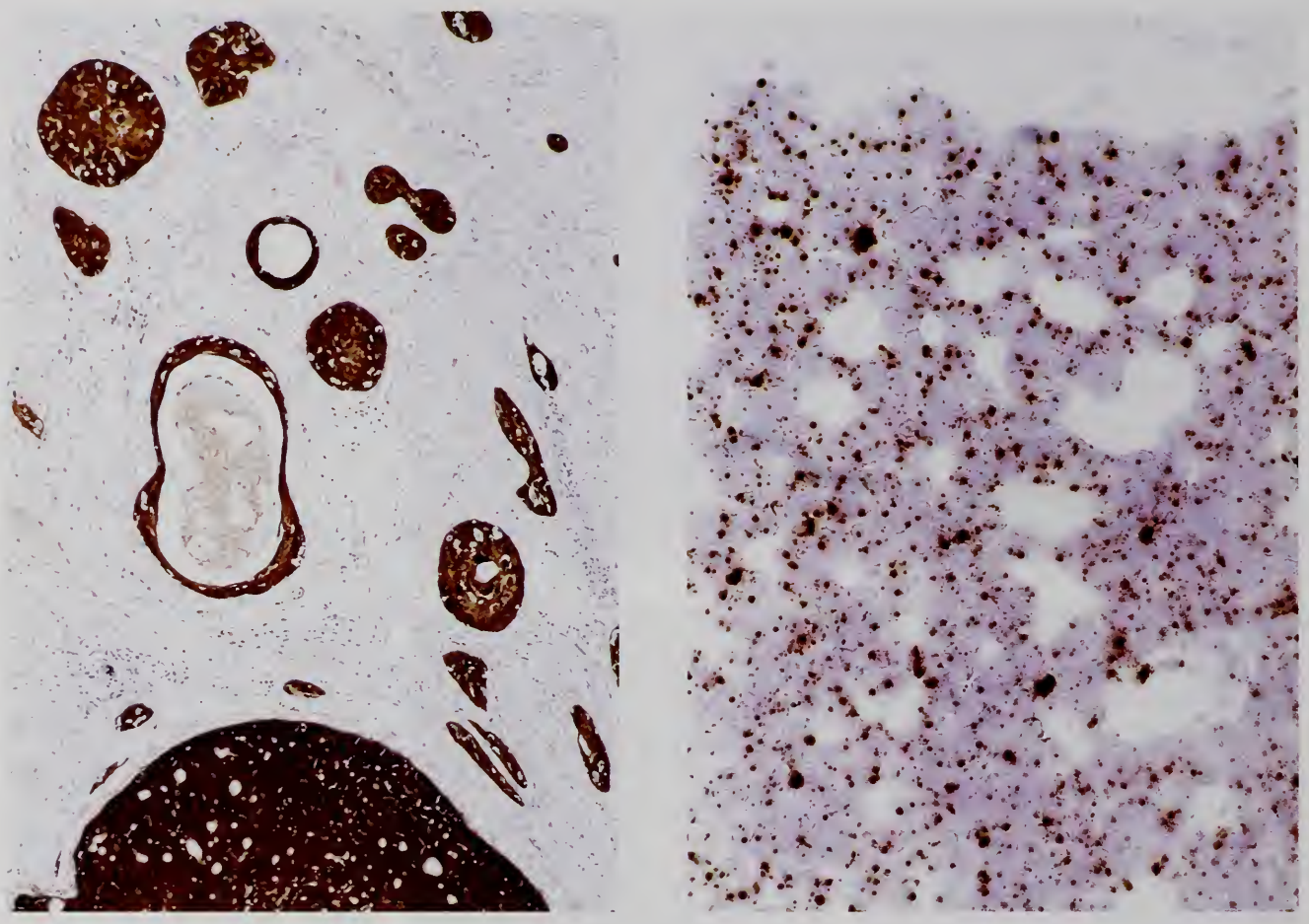


Figure 5-125

ADENOID BASAL CELL TUMOR: EPITHELIOMA WITH MIXED ADENOID CYSTIC AND SQUAMOUS CELL CARCINOMA

Left: Both the epithelioma and carcinoma components of the tumor in figure 5-124 exhibit diffuse expression of p16, which correlates with the presence of high-risk HPV.

Right: In situ hybridization demonstrates the presence of HPV 16.

occasionally associated with polypeptide hormone production. A few paraendocrine syndromes have been reported in association with small cell carcinoma of the cervix, including Cushing syndrome (245), carcinoid syndrome, and Eaton-Lambert myasthenic syndrome (392). Ectopic secretion of ADH, insulin, and calcitonin also have been described, but it is not possible to determine whether the carcinomas responsible were small cell carcinomas, squamous cell carcinomas composed of small cells, or poorly differentiated adenocarcinomas with neuroendocrine features. HPV type 18 is found in most small cell carcinomas with neuroendocrine granules, and HPV type 16 has also been reported (14).

Gross Findings. Small cell carcinoma is more often ulcerative and infiltrative than squamous or adenocarcinoma of the cervix. A barrel-shaped cervix is often present.

Microscopic Findings. Small cell carcinoma is highly cellular, composed of sheets of densely packed small cells with scant cytoplasm, and is identical to its counterpart in the vagina. In some examples, minor areas of glandular or squamous differentiation occur, but these, by definition, are less than 5 percent of the tumor. Nuclei are round to oval or slightly spindle shaped, and densely hyperchromatic. Nuclear detail and nucleoli are frequently obscured by smudging of the nucleus and typically there is extensive crush artifact. The cytoplasm is scant and finely stippled. Cell outlines, like the nuclei, are spindle to oval (fig. 5-126). A few pleomorphic larger cells with more irregular nuclei and one or more nucleoli may be present. Mitotic

activity is prominent, with three or more mitotic figures usually evident in each high-power field. Areas of necrosis are common. Capillary space invasion is observed in 60 to 90 percent of cases (414,416).

Immunohistochemical and In Situ Hybridization Findings. Nearly all neoplasms stain immunohistochemically for keratin and about one third to half stain for one or more markers of endocrine granules such as chromogranin, synaptophysin, serotonin, or somatostatin (fig. 5-126) (409,416). Neuron-specific enolase is nonspecific but in this setting is a reliable marker of neuroendocrine differentiation; nearly all small cell carcinomas stain for it, as well as for CD56.

Differential Diagnosis. Distinguishing small cell carcinoma from other poorly differentiated neoplasms of the cervix is difficult because the features of small cell carcinoma overlap with those of nonkeratinizing squamous cell carcinoma composed of small cells and poorly differentiated adenocarcinoma with neuroendocrine features. This is particularly true in small biopsies. A diagnosis of small cell carcinoma should be limited to a small cell neoplasm in which squamous or glandular differentiation is minor or inconspicuous, i.e., less than 10 percent of the tumor. If 10 percent or more of the tumor has gland formation, a ribbon-like or trabecular pattern, or rosettes, the neoplasm should be regarded as a mixture with a component of adenocarcinoma or simply designated an adenocarcinoma with neuroendocrine features if trabecular areas are evident. Similarly, if 10 percent or more of the tumor has squamous differentiation, the tumor should be regarded as a mixture with a component of squamous cell carcinoma (fig. 5-127). These neoplasms may contain neurosecretory granules.

Treatment and Prognosis. The usual treatment is radical hysterectomy and bilateral pelvic and paraaortic lymphadenectomy. Pelvic radiation is given to patients with nodal metastases. Metastasis occurs relatively early and frequently in the course of the disease compared with ordinary cervical carcinoma. Lymph node metastasis is present in more than half of the patients with small cell carcinomas less than 2 cm in diameter and in a higher proportion of those with larger lesions (414,416). At least 40 percent of patients with stages I and II disease have recurrences, compared to about 30 percent of patients with other forms of cervical carcinoma of the same stages (416). In one study of 15 cases, only 3 patients were free of tumor (127). In another study, 12 of 14 women died of tumor even though most of the tumors were stage I or II (365). Distant metastasis to organs such as lung, liver, brain, and bone is common. Small cell carcinoma is a highly aggressive tumor, and with rare exception, only women with tumor confined to the cervix are likely to survive. Combination chemotherapy is added to the treatment for patients with stage II and higher tumors, but metastases are seldom treated successfully (168).

Large Cell Neuroendocrine Carcinoma

Among neuroendocrine tumors of the cervix, *large cell neuroendocrine carcinoma* (LCNC) is the most recently recognized. In the past these tumors were classified as atypical carcinoids and variants of small cell carcinoma, and probably many were misclassified as poorly differentiated adenocarcinomas or large cell nonkeratinizing squamous cell carcinomas.

The clinical presentation is nonspecific. The diagnosis is suspected when a tumor is composed of sheets of medium to large cells displaying an insular or trabecular growth pattern. Glands are detected within the nests of cells and a component of adenocarcinoma is a common finding. In one study, AIS was found adjacent to the tumor in two thirds of the cases (132). These tumors have a high mitotic index (over 10 mitotic figures per 10 high-power fields) and, frequently, extensive geographic necrosis and lymphvascular space invasion (fig. 5-128) (351). Chromogranin appears to be the best immunohistochemical stain to confirm the diagnosis, as it is positive in a least 25 percent of cells in all cases thus far reported.

The differential diagnosis includes poorly differentiated squamous cell carcinoma and adenocarcinoma. In contrast to LCNC, squamous cell carcinoma usually displays some evidence of keratinization and lacks organoid, palisading, and trabecular patterns. Squamous and adenocarcinomas do not display the characteristic immunoprofile of LCNC. In contrast to other typical and atypical carcinoids, LCNC

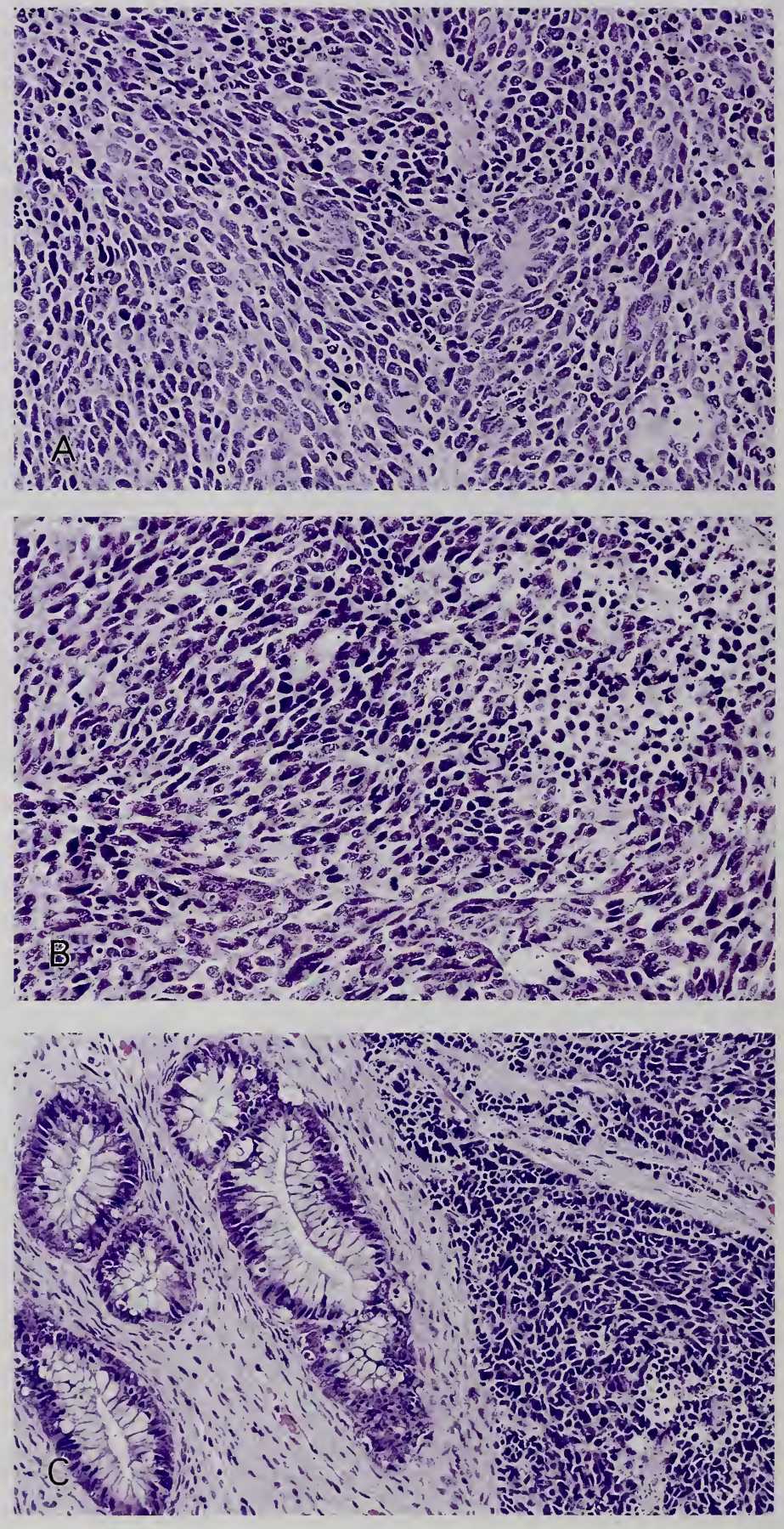


Figure 5-126

SMALL CELL CARCINOMA

A: The solid tumor is composed of cells with enlarged atypical hyperchromatic nuclei with nuclear molding and minimal cytoplasm. Numerous mitotic figures are present. The tumor is predominantly undifferentiated but shows a small rosette-like structure.

B: Atypical nuclei are molded together and have a spindled appearance; cellular necrosis is present.

C: The tumor is associated with AIS, intestinal type and both lesions contained HPV 18 by in situ hybridization.

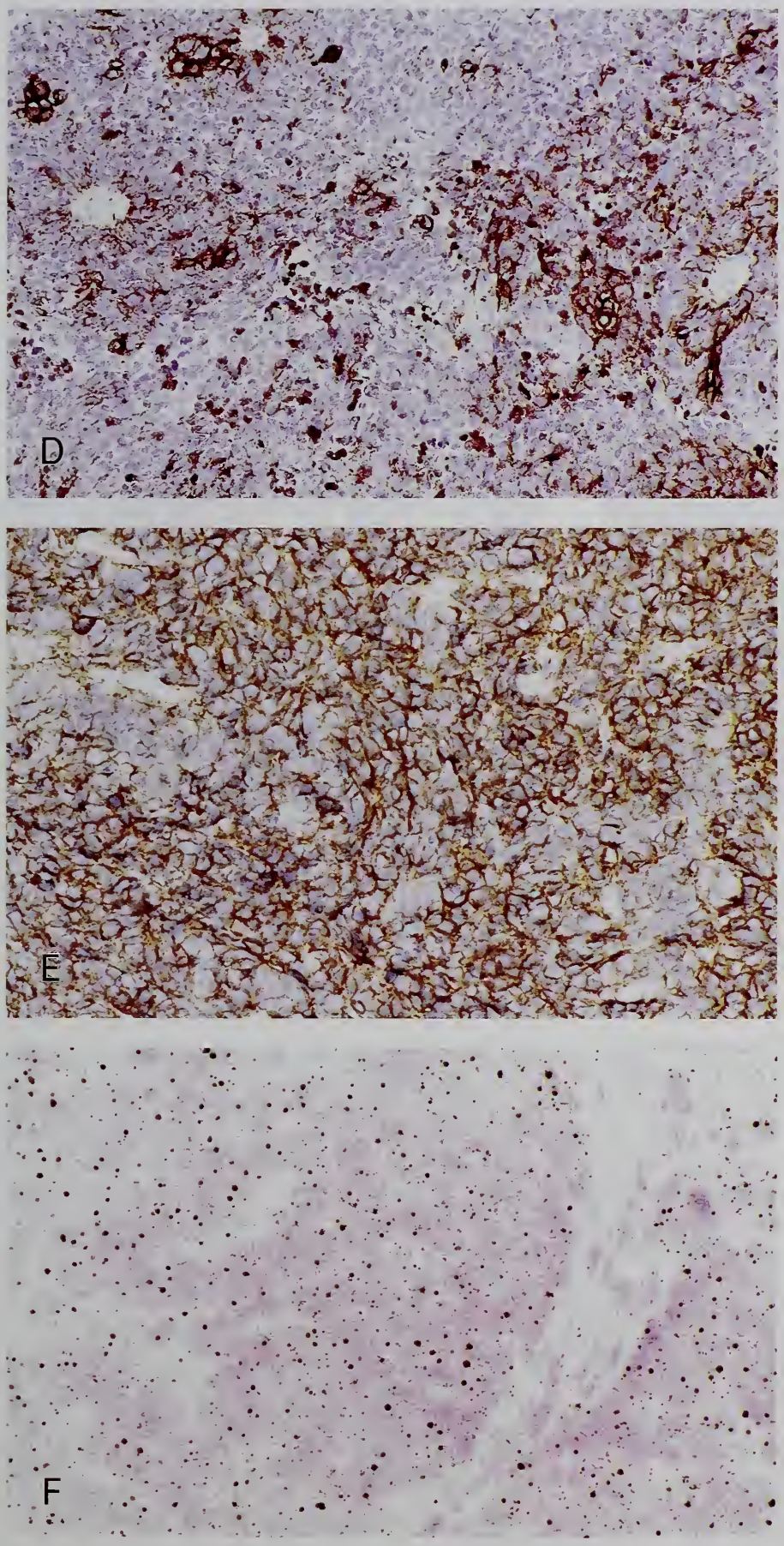


Figure 5-126 (Continued)

D: Tumor partially expresses cytokeratin AE1/AE3.

E: Tumor diffusely expresses CD56.

F: In situ hybridization demonstrates the presence of HPV 18.

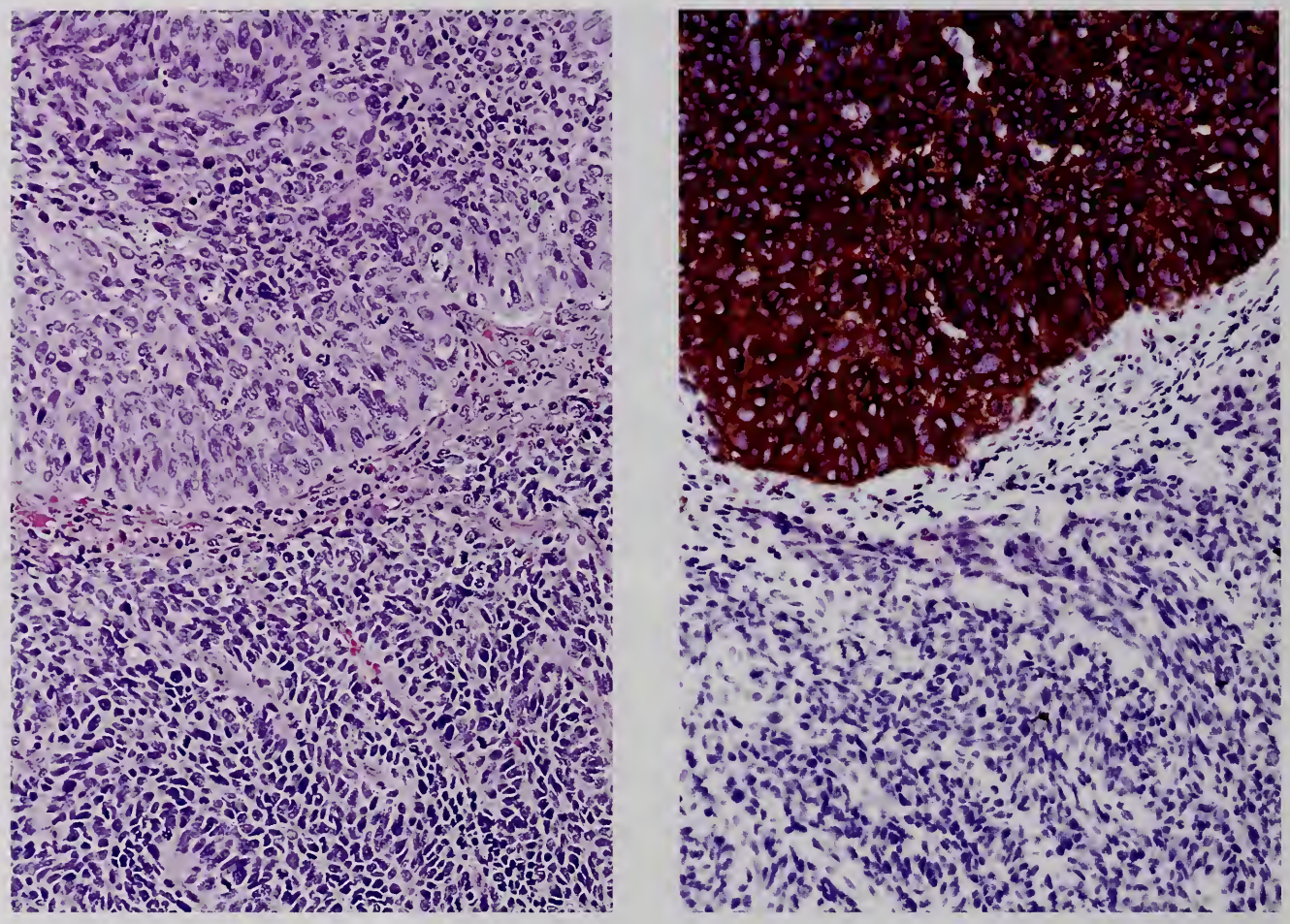


Figure 5-127

SMALL CELL CARCINOMA WITH SQUAMOUS CELL CARCINOMA

Left: A nest of small cell carcinoma consists of cells with minimal cytoplasm whereas the cells in the adjacent nest of squamous cell carcinoma have more abundant eosinophilic cytoplasm.

Right: Squamous carcinoma diffusely expresses cytokeratin AE1/AE3 whereas the small cell carcinoma component is negative.

has a higher mitotic index and more extensive necrosis. Small cell carcinomas are composed of smaller cells with scant cytoplasm and hyperchromatic nuclei; they are less likely to be positive for chromogranin and neuron-specific enolase. LCNC should also be distinguished from LCNC metastatic from other sites, notably the lung, but metastasis to the cervix is rare.

These are highly aggressive tumors for which optimal therapy has not yet been determined. Treatment generally has been similar to that for cervical and pulmonary small cell carcinoma (229).

UNDIFFERENTIATED CARCINOMA

All carcinomas that lack specific differentiation are placed in this category.

MESENCHYMAL TUMORS

Mesenchymal tumors involving the cervix are similar to those involving other sites. The reader is referred to the Fascicle *Tumors of the Soft Tissues* (208a) regarding the general morphologic, immunohistochemical, and ultrastructural features of these tumors.

Mesodermal Stromal Polyp (Pseudosarcoma Botryoides)

Mesodermal stromal polyps arise in the exocervix of women of reproductive age, particularly in pregnant women. They are much less common in the cervix than in the vagina, where they were initially described and designated vaginal polyps (see chapter 6) (295).

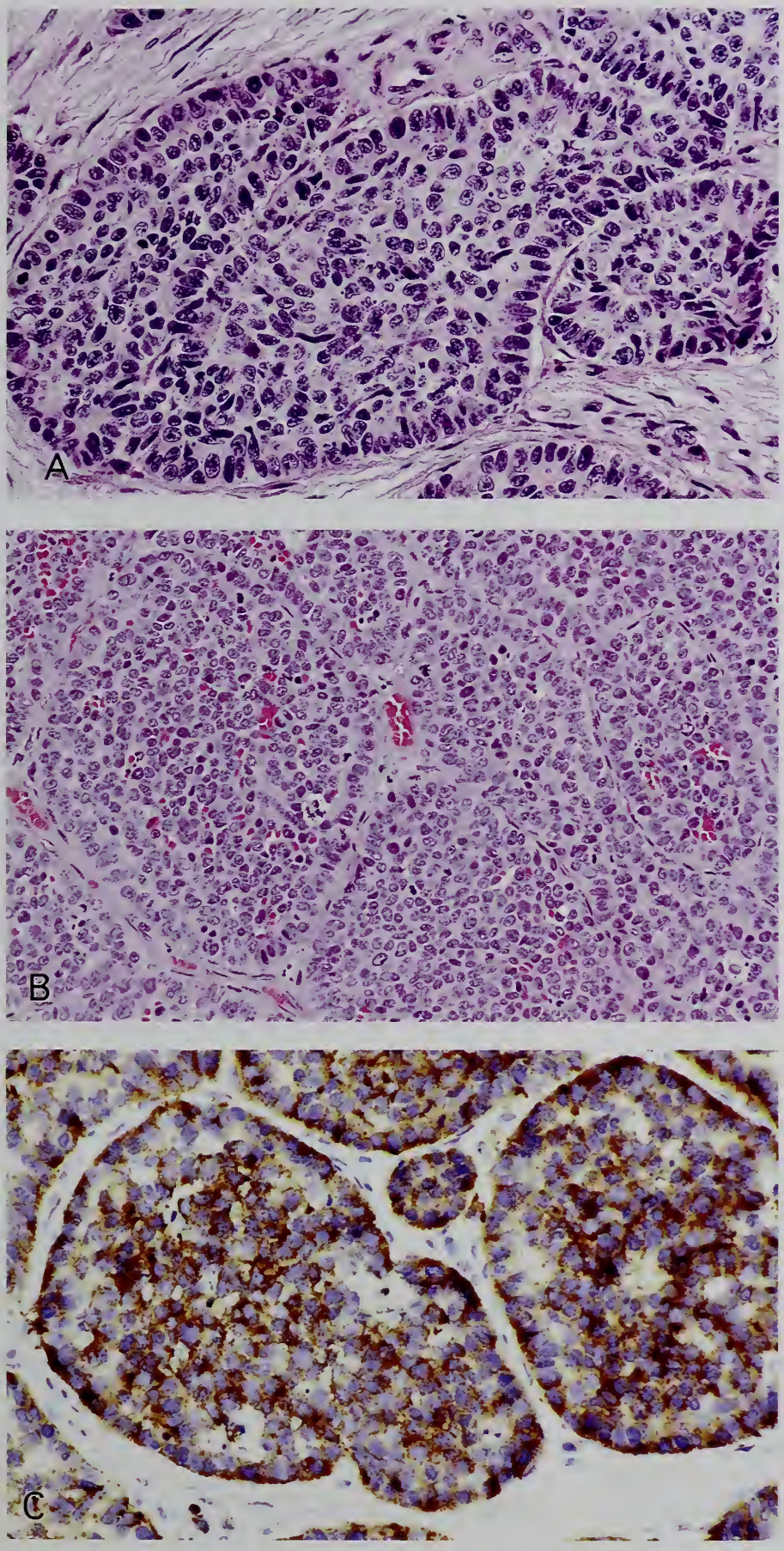


Figure 5-128

LARGE CELL NEUROENDOCRINE CARCINOMA

A: Islands of tumor cells with peripheral palisading have granular chromatin, suggesting a carcinoid tumor, but nuclear pleomorphism and diffuse infiltration are consistent with carcinoma.

B: Nests of tumor cells in an insular pattern with peripheral palisading have notable nuclear atypia, numerous mitotic figures, and numerous apoptotic bodies.

C: The tumor cells diffusely express synaptophysin.

An exophytic lesion, mesodermal stromal polyp is composed of edematous stroma covered by squamous epithelium. Scattered within the stroma are small spindle-shaped cells with scant cytoplasm and bland nuclei. The stroma may also contain occasional enlarged multinucleate hyperchromatic fibroblasts that may have an alarming appearance, particularly in a patient at term (72). Unlike sarcoma botryoides, the lesion is not characterized by dense cellularity or a cambium layer, mitotic figures are rare, and rhabdomyoblasts are absent. The lesion is benign but may recur if incompletely removed.

Leiomyoma

Leiomyomas occur in the cervix in about 8 percent of women whose uteri contain leiomyomas. Most cervical leiomyomas are asymptomatic, but some produce vaginal bleeding or discharge. Large cervical leiomyomas protrude below the os, fill the vagina, and may cause inversion of the uterus.

Grossly, leiomyomas are typically discrete and firm, and have a whorled appearance on sectioning. Microscopically, they are the same as those in the myometrium. Superficial erosions, edema, and infarction are more common in cervical leiomyomas than in those of the corpus. Increased mitotic activity may occur in those that are prolapsed or ulcerated. In these, the mitotic activity is highest in a narrow zone, beneath the ulcer, but even in this zone it seldom exceeds 4 mitotic figures per 10 high-power fields. Lipomatous differentiation may occur but is more common within leiomyomas in the uterine corpus.

Other Benign Mesenchymal Tumors

Both *capillary hemangiomas* and *cavernous hemangiomas*, as well as *arteriovenous malformations* occur in the cervix (9,129,150). The malformations are generally small and secondary to biopsy or conization but may be part of a larger pelvic vascular abnormality.

Primary *benign schwannomas* of the uterine cervix have been reported (71), including one with pigment (401). *Lipomas* and *lipoleiomyomas* occur in the cervix and are similar to those of the uterine corpus. *Paragangliomas* are identified by their nesting arrangement, mixed population of chief and sustentacular cells, and endocrine granules (443). Individual cases of *ganglioneuroma* and *rhabdomyoma* have also been described (71).

Leiomyosarcoma

Leiomyosarcoma is the most common primary sarcoma in the cervix (6), although only 20 cases have been reported (32). Most leiomyosarcomas of the cervix are buried within reports of leiomyosarcoma of the uterine corpus. Rare examples of myxoid, xanthomatous, and epithelioid cervical leiomyosarcomas have been reported (32,78,115,121,344). The youngest reported patient was 36 years of age (344). Leiomyosarcoma of the cervix usually arises in perimenopausal women who present with vaginal bleeding. Like other primary malignant tumors of the cervix, leiomyosarcoma may develop in a cervical stump after subtotal hysterectomy (344).

Grossly, leiomyosarcomas are polypoid but, in contrast to leiomyomas, are larger and softer, and have a more irregular outline. They are more likely to contain areas of hemorrhage and necrosis.

Microscopically, leiomyosarcoma is composed of densely arranged interlacing bundles of smooth muscle cells with large, hyperchromatic, irregular nuclei. The microscopic criteria for leiomyosarcoma of the cervix are the same as for leiomyosarcoma of the uterine corpus. At least two of three features, namely, marked nuclear atypia, a mitotic index of greater than 10 mitotic figures per 10 high-power fields, and tumor cell necrosis, are required, except for the rare myxoid leiomyosarcoma in which the mitotic index is lower. Immunostains for desmin are helpful in cases in which the smooth muscle nature of the tumor is in doubt. Stromal sarcomas can be differentiated by the use of immunostains for CD10. Some smooth muscle tumors may express CD10. Accordingly, a panel of markers that includes desmin and caldesmon should be used when stromal versus smooth muscle differentiation is being evaluated. Postoperative spindle cell nodules may simulate leiomyosarcoma but are smaller, lack abnormal mitotic figures and necrosis, and do not display marked cytologic atypia. A history of a previous surgical procedure helps in establish the correct diagnosis.

The treatment is the same as for leiomyosarcoma of the corpus. Survival is poor (6,344).

Endometrioid Stromal Sarcoma, Low Grade

Low-grade endometrioid stromal sarcoma is a rare cervical tumor with features of low-grade endometrial stromal sarcoma of the uterine corpus (60,351). The tumor may arise from endometriosis. It should be distinguished from a primary low-grade endometrial stromal sarcoma involving the cervix secondarily.

Undifferentiated Endocervical Stromal Sarcoma

Undifferentiated endocervical stromal sarcoma is an endocervical stromal sarcoma that does not resemble a low-grade endometrial stromal sarcoma (2,179). Twelve cases were reported by Abell and Ramirez (6). The patients ranged in age from 29 to 72 years, with an average of 54 years. All presented with vaginal bleeding, and some complained of pain. The tumors formed polypoid masses that protruded into the endocervical canal and infiltrated the wall of the cervix. Surface necrosis and hemorrhage were prominent. Microscopically, the tumors were composed of uniform, small spindle cells with angular, ill-defined outlines and tapered ends. The neoplasms resembled endometrial stromal sarcomas to some extent but without the prominent background vascularity. In addition, the stromal proliferation tended to surround endocervical glands as occurs in adenosarcomas. Mitotic activity was high, usually exceeding 10 mitotic figures per 10 high-power fields. In the report of Abell and Ramirez, 6 of the 12 patients died of tumor.

Sarcoma Botryoides (Embryonal Rhabdomyosarcoma)

Definition. *Sarcoma botryoides* is a type of *embryonal rhabdomyosarcoma* characterized by grape-like clusters and an edematous myxoid background usually containing rhabdomyoblasts. A subepithelial cellular layer is characteristic.

General Features. Sarcoma botryoides usually arises in the vagina, but it may arise in the cervix (301). Sometimes it is not possible to assign a primary site to a bulky tumor that involves both organs simultaneously. Older reports, summarized by Ober (301), obscure the fact that sarcoma botryoides of the cervix has a different clinical profile and prognosis from that of the vagina.

Clinical Features. In contrast to sarcoma botryoides of the vagina, which is confined to infants and young children, sarcoma botryoides of the cervix can occur in older women. We have seen a few examples in women in their late 40s to early 50s and are aware of a woman in her 80s who was diagnosed with this neoplasm. Although some patients present with a polypoid grape-like mass, this classic presentation occurs more often with the vaginal sarcoma. Patients present with vaginal bleeding and some describe having passed tissue.

Gross Findings. Sarcoma botryoides forms multiple, pedunculated or sessile, soft grape-like clusters or single, multiple, and bilobed polyps covered by a glistening translucent surface. The sectioned surfaces vary from grayish white to light tan, with punctate areas of hemorrhage. A stalk or pedicle is common.

Microscopic Findings. The surface is usually focally ulcerated and there is a zone of increased cellularity (cambium layer) beneath the surface epithelium and around entrapped endocervical glands (fig. 5-129). The stroma beneath the epithelium, however, may not necessarily be overtly sarcomatous. Associated inflammation may create the erroneous impression of a chronic inflammatory, rather than neoplastic, process. The cells in the cambium layer are plump and spindle shaped, with hyperchromatic nuclei and scant cytoplasm.

Most sarcoma botryoides tumors contain rhabdomyoblasts. These are large elongated cells with abundant eosinophilic cytoplasm, with and without cross striations. Immunohistochemical stains for desmin and muscle-specific actin establish that these are muscle cells but myoglobin and myogenin confirm that they are rhabdomyoblasts.

Deep to the cambium layer, the tumor is less cellular, with the cells loosely dispersed in an edematous or myxomatous stroma. Apart from the cambium layer, the stroma is usually vascular and edematous, and is highly variable in cellularity. The mitotic rate in the most cellular areas ranges from 2 to 12 mitotic figures per 10 high-power fields (95). Cartilaginous differentiation is a minor feature in about half of the cases. The grape-like areas evident clinically result from edema and myxoid change.

Differential Diagnosis. Sarcoma botryoides must be distinguished from adenosarcoma and an edematous mesodermal cervical polyp akin to those in the vagina (pseudosarcoma

botryoides). Adenosarcoma is found in young women and typically displays condensation of stromal cells beneath the surface epithelium and around glands that may resemble the cambium layer of sarcoma botryoides. Adenosarcoma, however, does not form grape-like clusters because the stroma is more fibrous and lacks the edematous aspect of sarcoma botryoides. Adenosarcoma also displays a prominent leaf-like pattern characterized by numerous epithelial-lined cysts and cleft-like invaginations of the surface, resembling cystosarcoma of the breast. In contrast, if glands are present within sarcoma botryoides, they are focal and entrapped rather than a component of the neoplastic process.

Edematous cervical mesodermal polyps resemble sarcoma botryoides but usually occur in adult women as solitary small, soft fleshy protuberances. They seldom exceed 1.5 cm in diameter. The edematous fibrous stroma of a polyp may resemble that of sarcoma botryoides, but a cambium layer or rhabdomyoblasts are not seen and the stroma is more uniform. Although polyps in pregnant women may contain atypical or multinucleated stromal cells, they are widely scattered and not part of a sarcomatous stroma (71,72,295).

Treatment and Prognosis. Sarcoma botryoides of the cervix is less aggressive than sarcoma botryoides of the vagina (93,300). In recent years, the outlook for patients has improved dramatically. Patients with localized disease exhibiting favorable prognostic features, such as a single polyp without deep invasion, can be effectively treated by organ-preserving surgery or simple hysterectomy. In these patients, the benefit of adjuvant chemotherapy is unclear. Women with unfavorable prognostic features seem to benefit from radical surgery and adjuvant chemotherapy (449).

Dermatofibrosarcoma Protuberans

These tumors are extremely rare in the cervix and vagina (fig. 5-130). For a detailed description see the Fascicle, *Tumors of the Soft Tissues* (206a).

Alveolar Soft-Part Sarcoma

Definition. *Alveolar soft-part sarcoma* (ASPS) is characterized by solid and alveolar groups of large epithelial-like cells with granular, eosinophilic cytoplasm.

General Features. More than 200 ASPSs have been reported since the initial description in 1952, but only 6 have been located in the cervix (3,112,113,222,347). The patients are between 30 and 40 years of age and generally present with bleeding. Five of the 6 had stage I disease. The origin of ASPS is uncertain: striated muscle, paraganglia, and nerve origins have all been suggested.

Gross Findings. ASPS forms a small, irregular, circumscribed, friable nodule on the cervix (3,347). The largest tumors reported were 4 cm in diameter (222).

Microscopic Findings. Microscopically, ASPS is relatively well demarcated, although small groups of cells may infiltrate the periphery. The tumor is composed of cellular nests that are generally centrally cavitated, resembling alveoli, and separated by thin vascular septa. The cells are uniform and polyhedral, with abundant eosinophilic granular cytoplasm and small nuclei with prominent nucleoli. The cytoplasm is usually strongly PAS positive and diastase resistant, and the presence of PAS-positive, diastase-resistant rod-like crystals in the cytoplasm (80 percent of tumors) is diagnostic.

Immunohistochemical Findings. Immunohistochemical examination shows myogenic characteristics in that muscle-specific actin and desmin are usually positive. In addition, a positive reaction with antibodies against neuron-specific enolase and S-100 protein has been described (3).

Differential Diagnosis. The main entities in the differential diagnosis are metastatic renal cell carcinoma, clear cell carcinoma, and paraganglioma. Only two paragangliomas have been reported in the cervix (443). Paraganglioma is distinguished from ASPS by the presence of solid nests of chief and sustentacular cells and cells containing neuroendocrine granules. Metastasis to the cervix from renal cell carcinoma is rare. In addition, renal cell carcinoma lacks immunologic evidence of a myogenic origin and it does not have the PAS-positive diastase-resistant crystals found in most ASPSs. Clear cell carcinoma has a tendency to form papillary processes and small cysts. The cells are clearer than in ASPS, with sparse PAS positivity in the cytoplasm. The PAS positivity in clear cell carcinoma dissolves with diastase digestion. Hobnail-appearing nuclear protrusions occur in clear cell carcinoma but are rare or absent in ASPS.

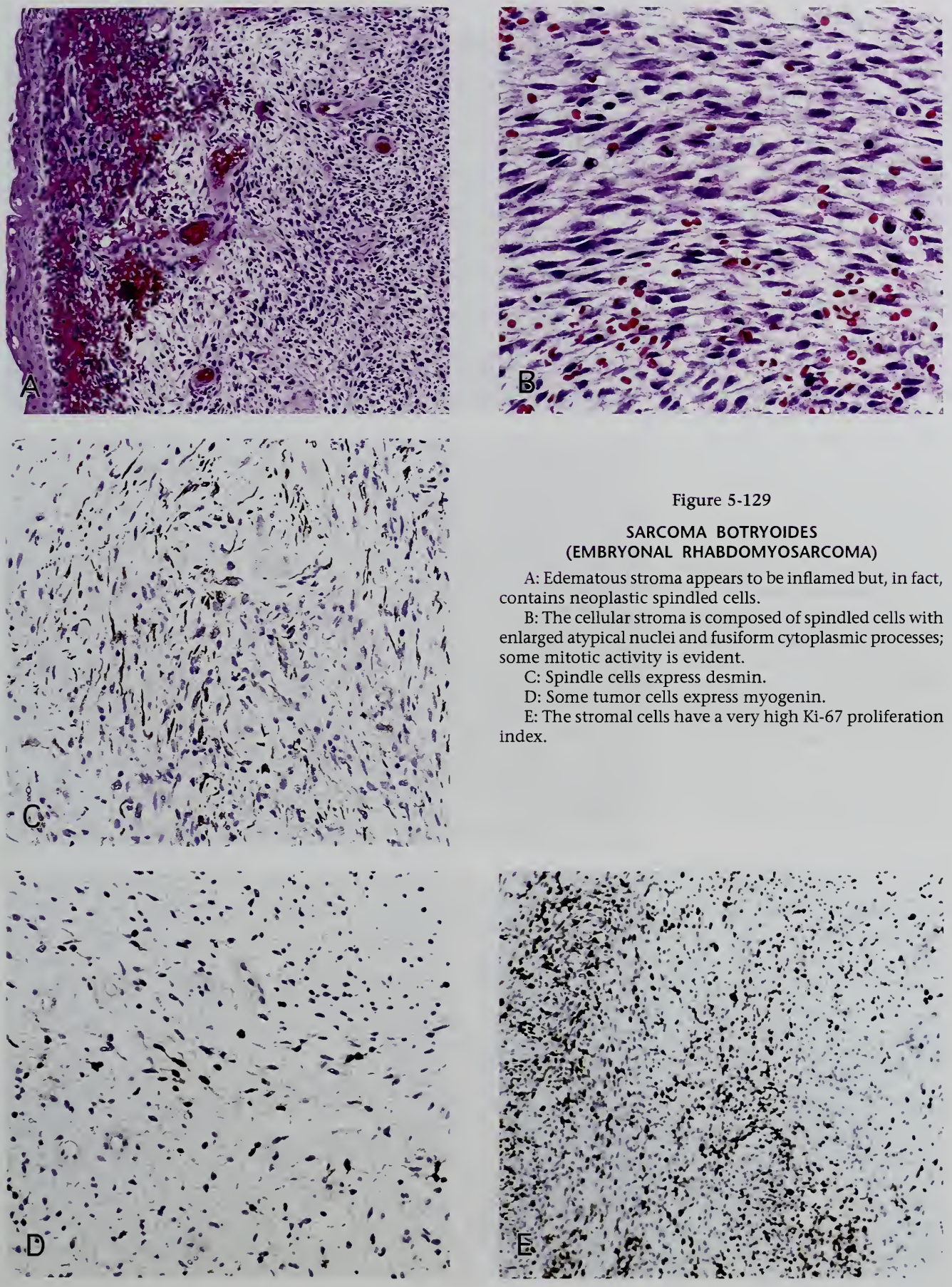


Figure 5-129

SARCOMA BOTRYOIDES (EMBRYONAL RHABDOMYOSARCOMA)

A: Edematous stroma appears to be inflamed but, in fact, contains neoplastic spindled cells.

B: The cellular stroma is composed of spindled cells with enlarged atypical nuclei and fusiform cytoplasmic processes; some mitotic activity is evident.

C: Spindle cells express desmin.

D: Some tumor cells express myogenin.

E: The stromal cells have a very high Ki-67 proliferation index.

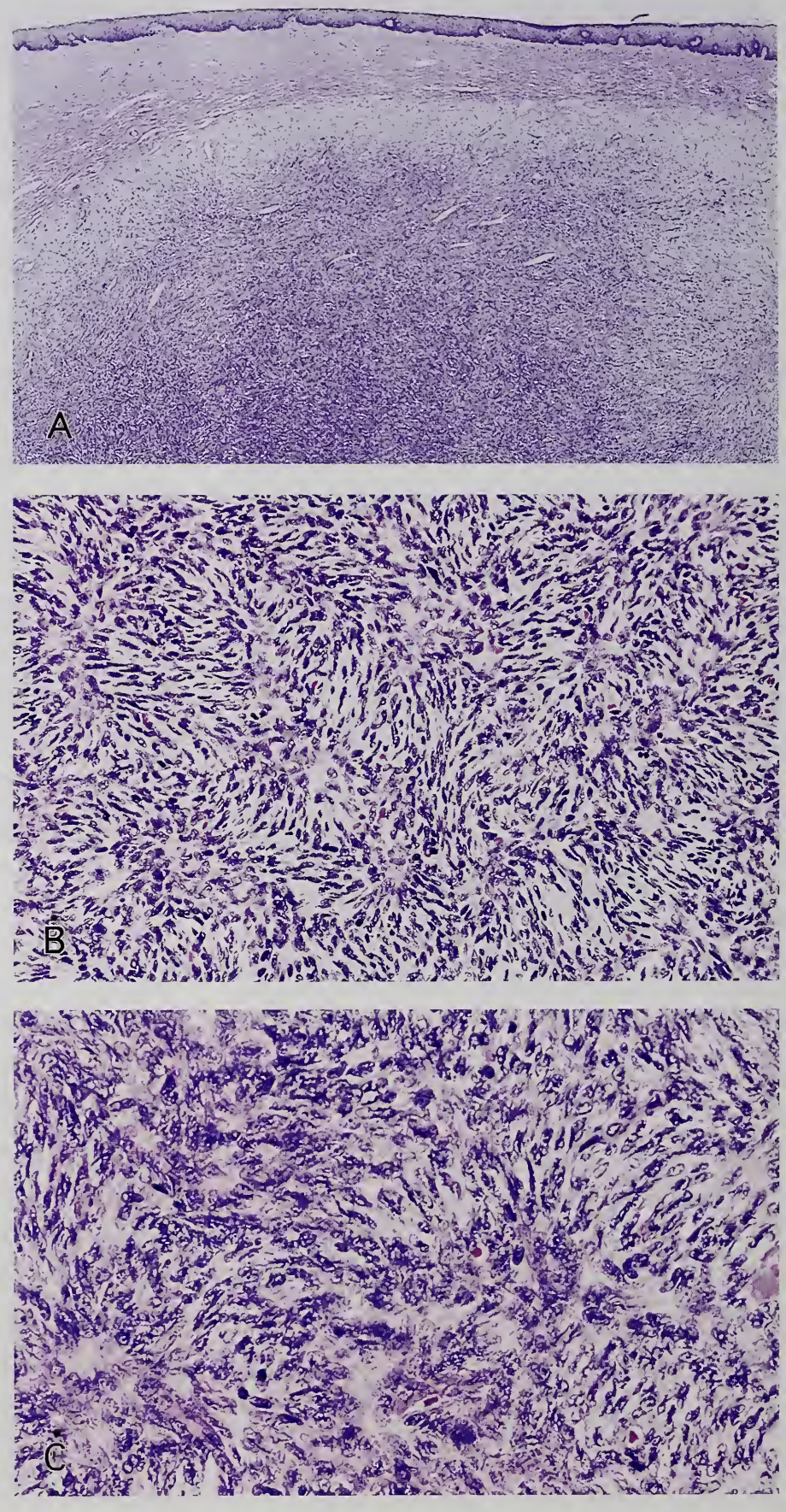


Figure 5-130

DERMATOFIBROSARCOMA PROTUBERANS

A: The tumor is a well-circumscribed cellular spindle cell lesion.

B: Spindle cells are in a storiform pattern.

C: Cellularity is dense and spindle cells have uniform elongated nuclei with minimal cytoplasm.

Treatment and Prognosis. Five of the 6 described patients (3,112,113,122,347) underwent hysterectomy with bilateral salpingooophorectomy and were free of tumor at last contact. Only one of these patients received adjuvant chemotherapy.

Osteosarcoma

A pure *osteosarcoma* has been described in the cervix (43), similar to what has been described in the uterine corpus (133). It occurred in a postmenopausal woman as a polypoid, fleshy, pinkish gray, 3-cm neoplasm. Microscopically, malignant spindle cells were admixed with atypical cells within lacunae of osteoid.

Osteosarcoma should be distinguished from a malignant mixed mesodermal tumor and leiomyosarcoma with osteoclast-like giant cells. In a malignant mixed mesodermal tumor, malignant glands are intermingled with a sarcomatous stroma. Thorough sectioning may be necessary to identify an epithelial component in a sarcoma containing heterologous elements.

Osteoclast-like giant cells occur within some uterine leiomyosarcomas, but osteoid does not accompany them. Immunostains for actin and desmin should identify smooth muscle differentiation within a leiomyosarcoma. Desmin immunostains are negative in an osteosarcoma, but actin may be present if there is myofibroblastic differentiation within osteosarcoma.

Other Malignant Mesenchymal Tumors

These tumors include *malignant peripheral nerve sheath tumors* (208), *liposarcomas* (395), *angiosarcomas* (352), and *malignant fibrous histiocytomas* (71). A *hemangiopericytoma* involving the cervix has been reported (57).

MIXED EPITHELIAL AND MESENCHYMAL TUMORS

Papillary Adenofibroma

Definition. *Papillary adenofibroma* is a benign tumor composed of epithelial and mesenchymal components.

General Features. Papillary adenofibromas are uncommon in the cervix. Originally described in 1971 (5), most occur in the endometrium (419). Those developing in the endocervix are less common but are similar to those of the endometrium. Of 10 adenofibromas of the uterus, only one arose from the cervix (448).

Gross Findings. Adenofibroma is papillary or sessile and protrudes into the endocervical canal. Some exceed 5 cm in diameter. Papillary adenofibroma is typically firm, rubbery, and tan-brown, with punctate areas of hemorrhage evident on the surface. The presence of small cysts on the sectioned surfaces imparts a spongy or mucoid appearance. Most are superficial and do not invade the underlying stroma.

Microscopic Findings. Papillary adenofibroma has a nodular surface with a lobulated papillary configuration. Broad, fibrous, relatively acellular fronds are formed. The surface is covered by flattened, nonspecific cuboidal epithelium that is not significantly proliferative. Columnar mucinous cells and squamous differentiation occur focally in some tumors. The nuclei of the stromal cells are small, uniform, and bland. Mitotic activity is minimal or absent; and there is no increased cellularity around entrapped glands.

Differential Diagnosis. The main entity in the differential diagnosis is adenosarcoma. Adenofibromas lack the stromal cellularity with condensation around glands of adenosarcoma. Also, in contrast to adenosarcoma, the stromal cells of adenofibroma have bland nuclei and little or no mitotic activity, and have more intervening fibrous tissue.

Treatment and Prognosis. Local excision is curative but the tumor may recur if incompletely excised.

Adenomyoma

Adenomyomas are composed mainly of endocervical mucinous glands surrounded by smooth muscle. Tumors composed of endometrial glands and surrounded by endometrial stroma and smooth muscle have also been described. Rarely, the glandular epithelium is sufficiently atypical to justify the diagnosis of *atypical polypoid adenomyoma*.

Patients range in age from 21 to 55 years (mean, 40 years). Generally, patients are asymptomatic. The tumors range in size from 1 to 25 cm and can prolapse through the external os or project into the pelvis without mucosal involvement. Microscopically, the glands are typically large and irregularly shaped. They are often

surrounded by smaller glands, creating a lobular pattern. Generally, tubal type epithelium is found in addition to the mucinous cells.

The main entity in the differential diagnosis is minimal deviation adenocarcinoma. In contrast to the latter, adenomyomas are well circumscribed with a lobular arrangement of the glands. In addition, there is no evidence of a desmoplastic reaction and there is no cytologic atypia. Patients have been successfully treated by "polypectomy" although in two cases "recurrence" after polypectomy required hysterectomy (131).

Adenosarcoma

Adenosarcoma is composed of a mixture of benign epithelial and malignant mesenchymal components. Patients range in age from 13 to 67 years, with a mean of 37 years, which is significantly younger than women with adenosarcomas arising in the uterine corpus, the majority of whom are postmenopausal (191).

Adenosarcomas in the cervix, as in the endometrium, are broad-based, sessile polypoid growths that enlarge and distort the uterus. Microscopically, papillary stromal fronds lined by epithelium form leaf-like processes that protrude into cysts and cleft-like spaces distributed within the stroma. The epithelium is varied, with a tendency to have more mucinous and squamous differentiation than in adenosarcomas of the endometrium. Adenosarcomas of the cervix, like those of the endometrium, are characterized by periglandular hypercellularity of the stromal component. The cellularity varies in different areas of the tumor. Differentiation to endometrial type stroma occurs in focal areas of some tumors, but the stromal component is usually devoid of specific features. Atypia in the stromal cells varies from mild to marked throughout the tumor, and the frequency of mitotic figures also varies from sparse to 1 or 2 per high-power field in higher-grade areas. Most adenosarcomas have 4 or more mitotic figures per 10 high-power fields (fig. 5-131). About 25 percent contain heterologous elements in the form of rhabdomyoblasts, fat, cartilage, and osteoid, and smooth muscle differentiation is found in some. Sarcomatous overgrowth can occur and some exhibit rhabdomyoblastic differentiation, simulating embryonal rhabdomyosarcoma (figs. 5-132–5-134).

The treatment of adenosarcoma is hysterectomy, but for young women with small localized tumors, cervical conization may suffice. These patients must be carefully followed because there is a risk of recurrence. Too few cases have been reported to evaluate the role of adjuvant chemotherapy (191).

Malignant Mixed Mesodermal Tumor (Carcinosarcoma)

Definition. *Malignant mixed mesodermal tumor* (MMMT) is a neoplasm composed of malignant epithelial and mesenchymal elements.

General Features. MMMTs primary in the cervix, both homologous (*carcinosarcoma*) and heterologous, are rare. They are much less common than MMMTs that develop in the uterine corpus. A recent study by Clement et al. (76) included a detailed analysis of 9 cases along with a literature review that included 14 additional cases. Most MMMTs involving the cervix represent extensions from the endometrium, because nearly 25 percent of endometrial MMMTs involve the cervix when initially seen.

Recent studies have provided compelling evidence that MMMTs of the uterine corpus should be classified as variants of carcinoma. Most molecular studies support a monoclonal origin of MMMTs, with subsequent divergent differentiation. A recent study that analyzed the allelic status of 17 MMMTs demonstrated shared allelic losses and retention among multiple individual carcinomatous and sarcomatous foci within 16 of the tumors (120). In conjunction with the observations that the behavior of these tumors is dictated by the carcinomatous component and immunohistochemical stains demonstrate keratin expression in the mesenchymal component, it has been proposed that MMMTs be classified as variants of carcinoma rather than as sarcomas (341). Although primary cervical MMMTs have not been analyzed in a similar fashion, it is likely that their pathogenesis is similar.

Presenting symptoms of cervical MMMT are the same as those of similar tumors arising in the corpus, and the mean age of the patients at diagnosis is identical (62 years). Some patients were irradiated for squamous cell carcinoma of the cervix years earlier (6). Unlike uterine MMMTs, which have extrauterine spread in 25 to 50 percent of cases, all but one of the cervical

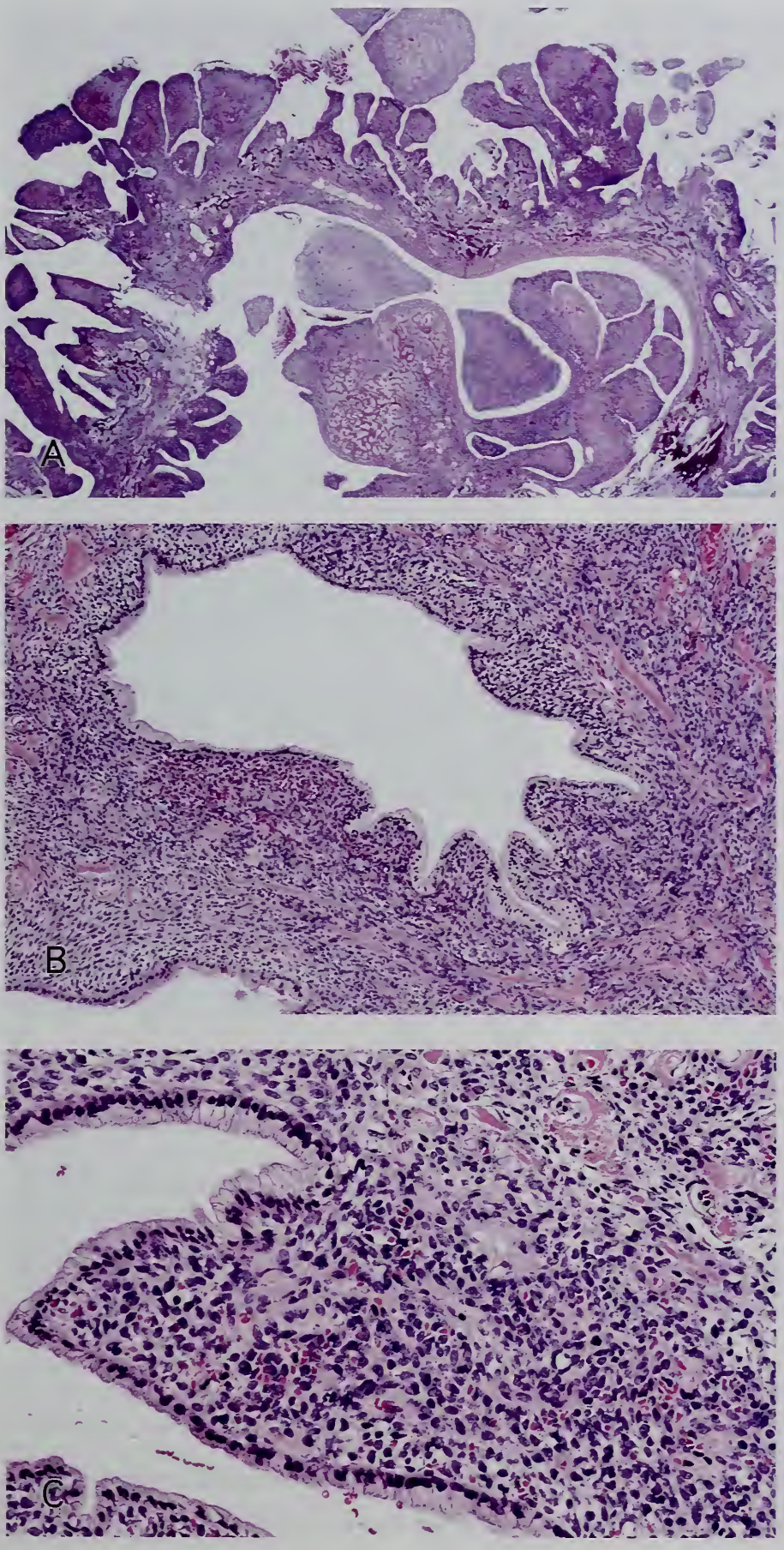


Figure 5-131

ADENOSARCOMA

A: The tumor is polypoid and forms clefted epithelial invaginations, creating a leaf-like pattern.

B: Histologically benign-appearing glandular epithelium is surrounded by cellular stromal proliferation.

C: Stromal cellularity is increased and condensed around glands. The cells are uniform and occasional mitotic figures are present.

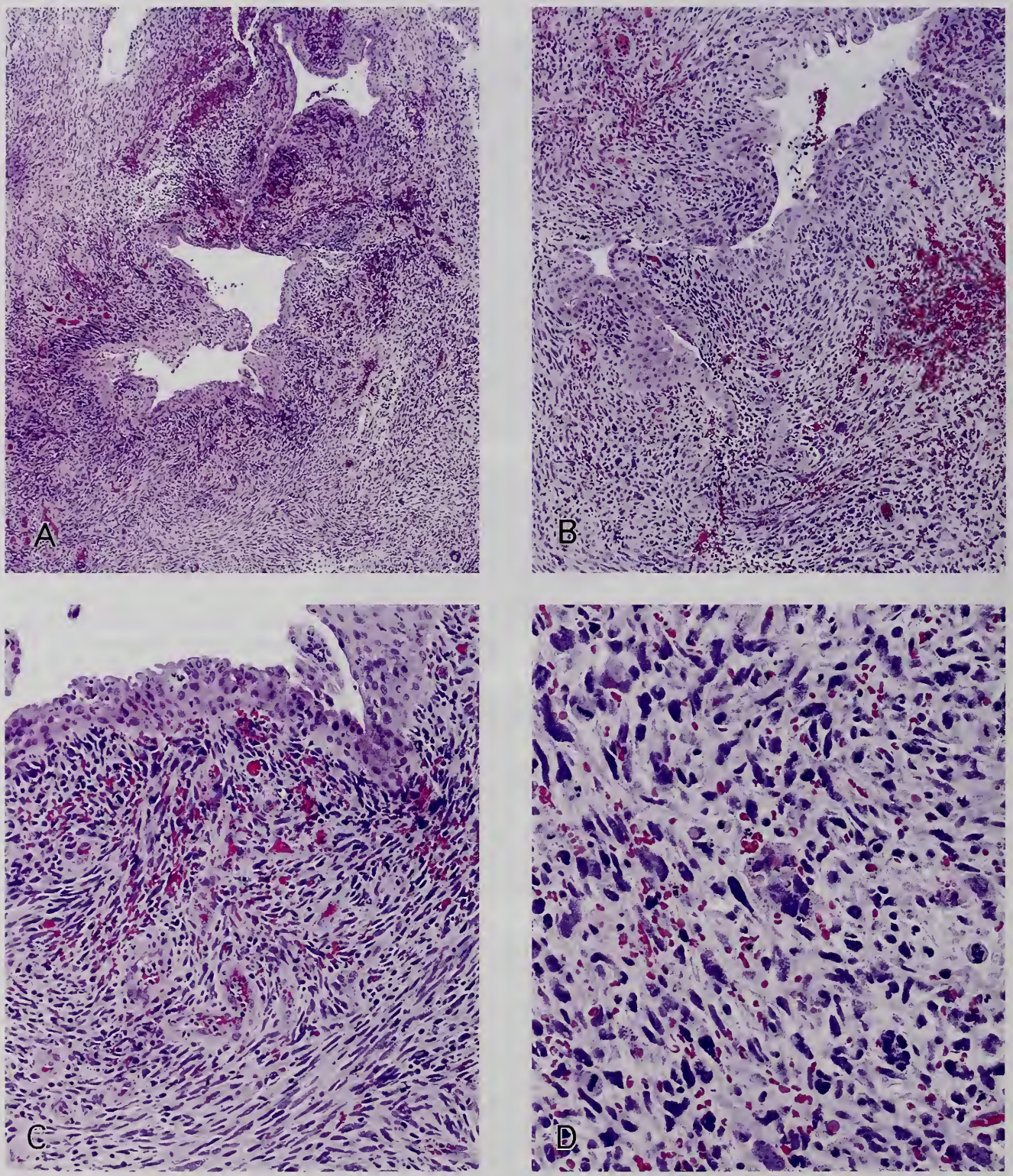


Figure 5-132

ADENOSARCOMA WITH SARCOMATOUS OVERGROWTH

A: Some regions of the tumor retain benign glands but other areas are composed of high-grade sarcoma.

B: High-grade sarcoma encroaches on benign glands.

C: High-grade sarcoma is composed of atypical spindle cells with enlarged hyperchromatic nuclei; numerous mitotic figures are present.

D: A region of pure sarcoma exhibits marked nuclear atypia; several mitotic figures are evident.

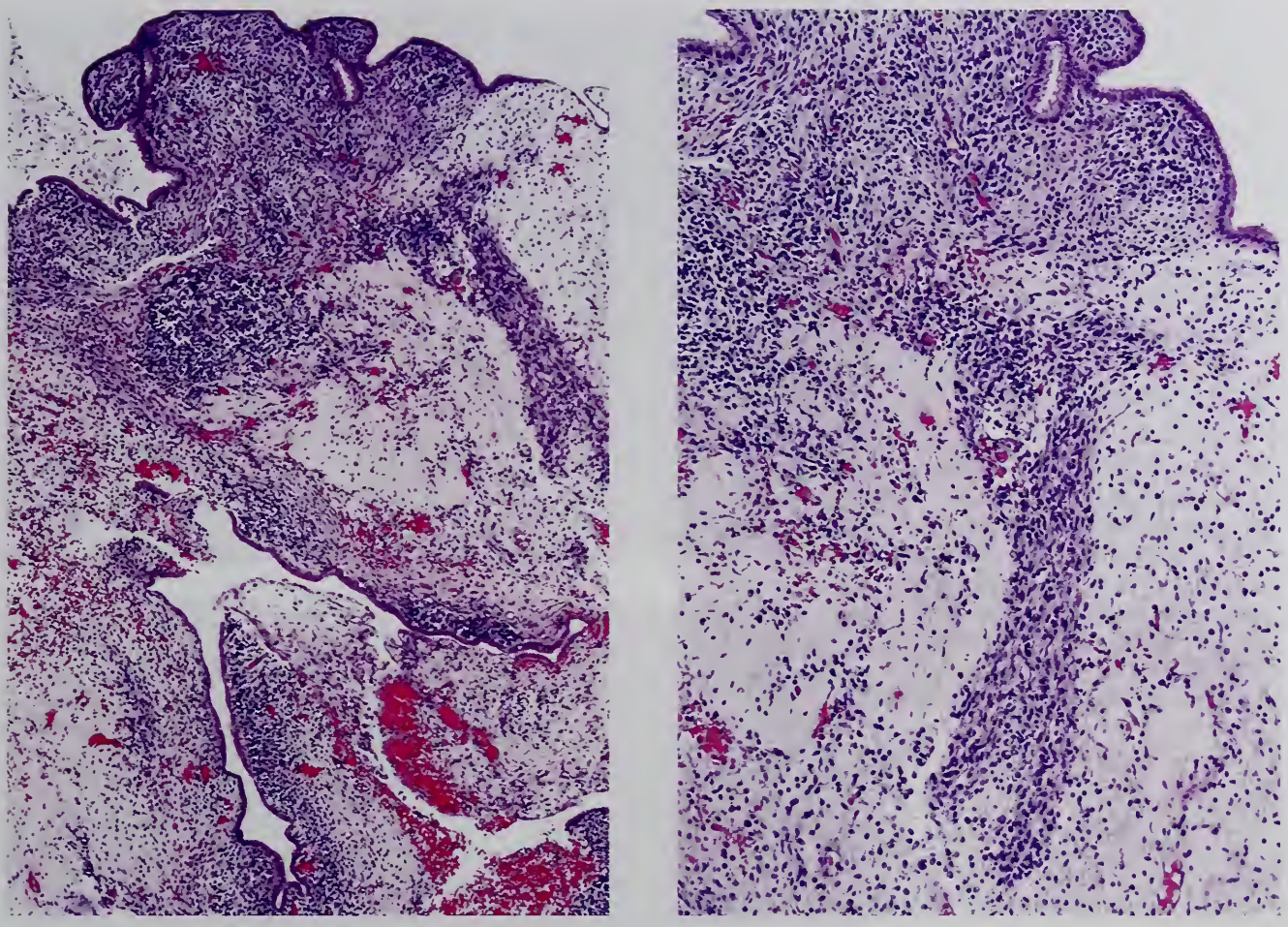


Figure 5-133

ADENOSARCOMA WITH RHABDOMYOBLASTIC DIFFERENTIATION

Left: Polypoid biphasic tumor exhibits the clefted architecture of adenosarcoma and has both hypercellular and edematous hypocellular regions.

Right: Subepithelial hypercellular stroma and a cellular fascicle of stromal cells are admixed with hypocellular stroma, reminiscent of embryonal rhabdomyosarcoma.

MMMTs in the report by Clement et al. (76) were stage IB (confined to the cervix).

Gross Findings. MMMT of the cervix forms a large, polypoid, partially necrotic mass that replaces the cervix.

Microscopic Findings. Like the uterine corpus counterpart, malignant glands are present along with sarcomatous differentiation, however, the carcinomatous component differs dramatically in the cervical as compared to the uterine corpus neoplasm. In cervical tumors, the carcinomatous component generally is a subtype of cervical carcinoma, not an endometrioid, serous, or clear cell carcinoma as occurs in the corpus MMMT. In a study by Clement et al. (76) the most frequent epithelial component was squamous cell carcinoma, in several cases the rare basaloid subtype. Other carcinomatous components included adenoid cystic and adenoid basal carcinomas. In their pure form both of these latter carcinomas are rare in the cervix and are rarely if ever associated with corpus MMMT. In contrast to the epithelial component, the sarcomatous component of cervical MMMT resembles the corpus counterpart, although there is a slightly lower frequency of heterologous components. Rhabdomyosarcoma and chondrosarcoma occur in MMMT (376), as well as liposarcomatous differentiation. In one unusual MMMT of the cervix, ganglion cells and glial tissue were identified (126). Fibroblastic differentiation is common, either low- or high-grade fibrosarcoma,

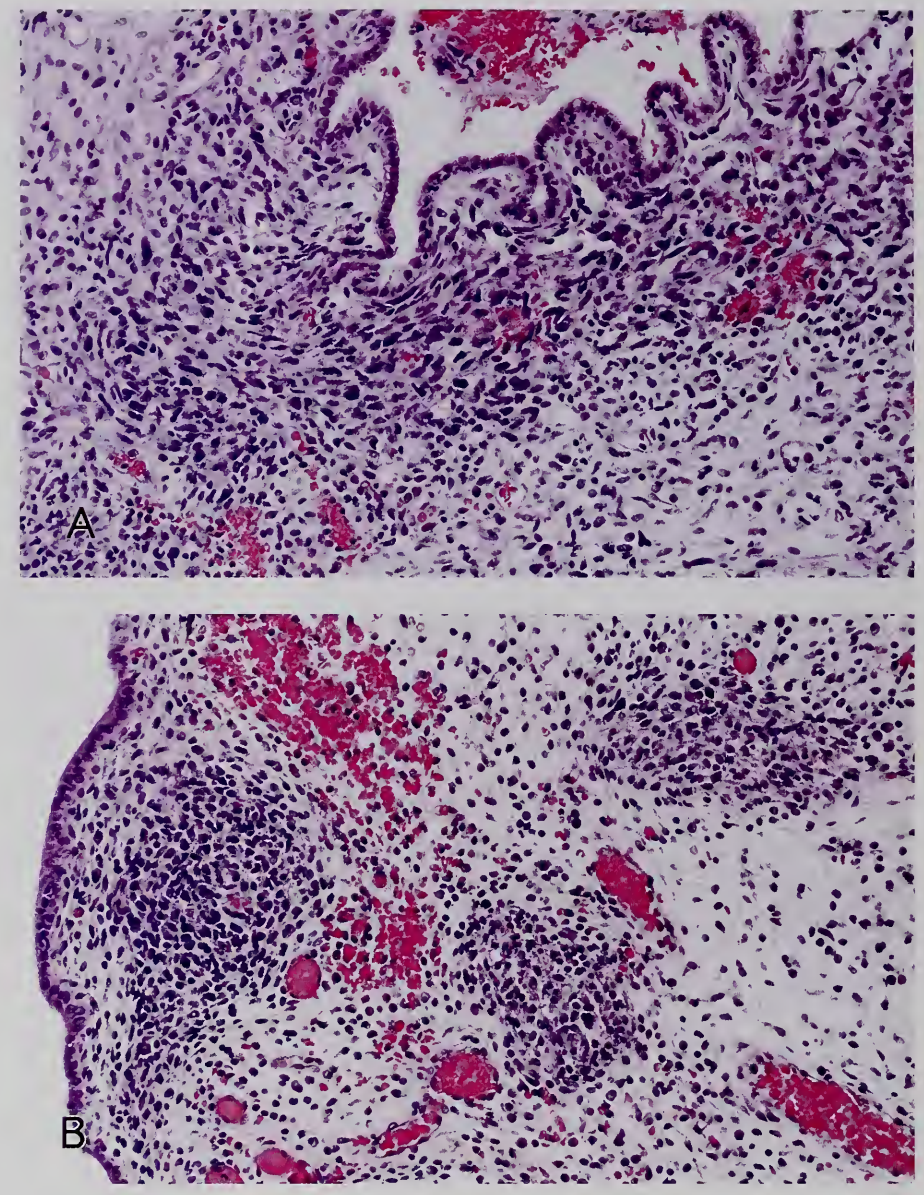


Figure 5-134

ADENOSARCOMA WITH RHABDOMYOBLASTIC DIFFERENTIATION

A: Periglandular stromal condensation is present.

B: Condensed stromal foci contain primitive atypical spindle cells and inflammatory cells.

and in some cases the sarcomatous component is a low-grade endometrial stromal sarcoma.

Treatment and Prognosis. The proportion of tumor-related deaths is lower than that for corpus MMMT. This may be due to the low stage at presentation of cervical MMMT. Therapy usually consists of hysterectomy and bilateral salpingo-oophorectomy and pelvic lymphadenectomy followed by combination chemotherapy or pelvic and abdominal irradiation, even if there is no evidence of metastasis.

Wilms Tumor

Wilms tumor in the cervix is similar to its renal counterpart. It is characterized by a triphasic pattern of epithelial, mesenchymal, and blastemal elements. Only a few cases have been reported in the cervix and these have usually been in adolescents (25,31,32,175).

The tumor presents as a polypoid mass partially filling the vagina and producing vaginal bleeding. Grossly, the neoplasm is gray, solid, and rubbery to gelatinous. Microscopically, it is composed of small cells with oval nuclei and scanty cytoplasm. A few admixed primitive tubules are present in a glomeruloid arrangement. Areas of fetal type skeletal muscle fibers with cross striations may be present along with smooth muscle fibers and islands of mature cartilage.

Wilms tumor is distinguished from MMMT by not containing areas of adenocarcinoma and by having glomeruloid differentiation and

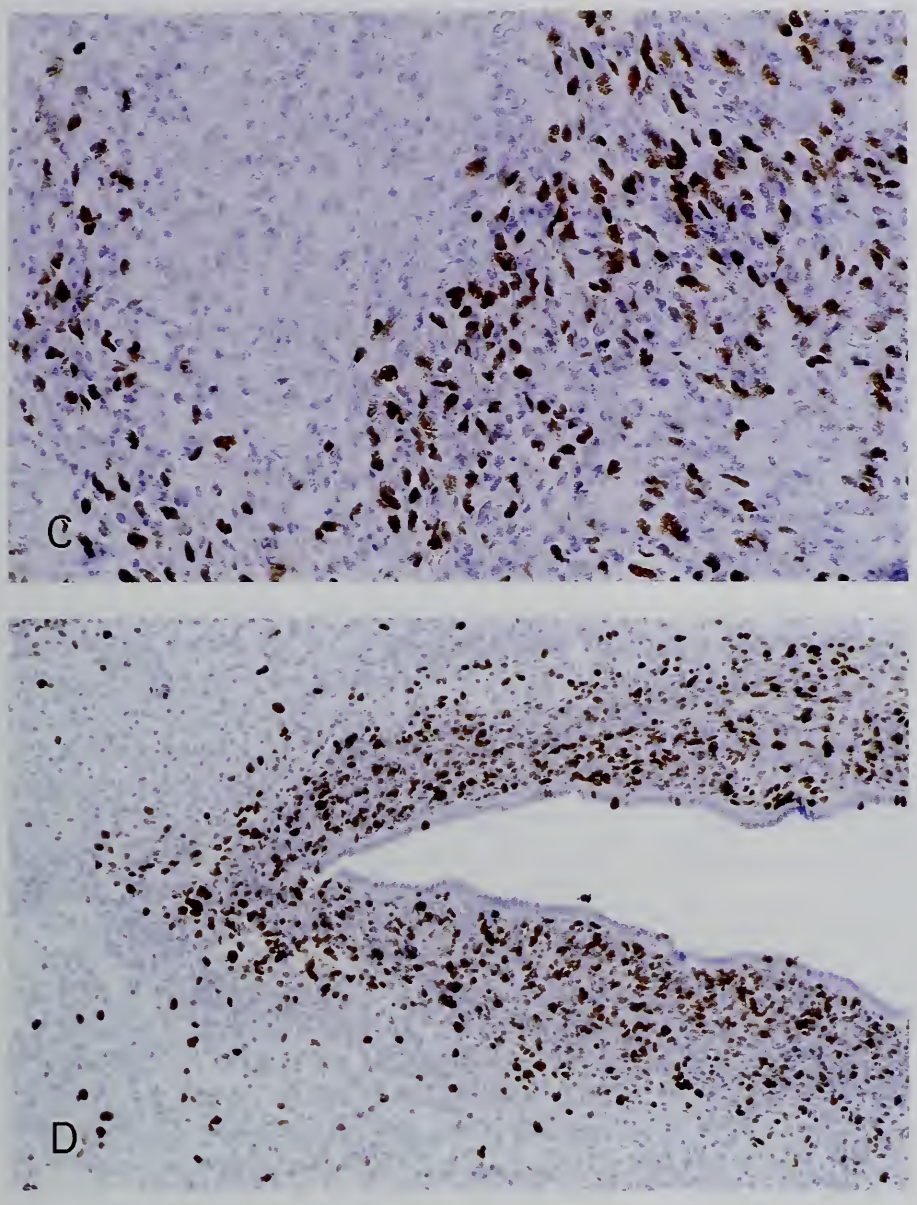


Figure 5-134 (Continued)

C: Stromal cells express myogenin, consistent with rhabdomyoblastic differentiation.

D: The periglandular stroma has a markedly increased Ki-67 proliferation index, much higher than seen in the usual low-grade stroma of a typical adenosarcoma.

tubules. Prolonged survival has been reported following local excision and chemotherapy. One patient (31) was well at last contact, 9.6 years after operation.

MISCELLANEOUS TUMORS

A variety of melanocytic lesions that commonly affect the skin occur on the cervix. These lesions are described in detail in dermatopathology textbooks. The following is a brief description of their appearance in the cervix, focusing on features that are distinctive for this location.

Melanocytic Nevus

Melanocytic nevi in the cervix are similar to those arising in the skin. They are rare in the cervix.

Blue Nevus

Definition. *Blue nevus* is a nevus composed of dendritic melanocytes that typically are heavily pigmented.

General Features. Blue nevus of the cervix was first described by Cid (68) in 1959, who subsequently found 9 examples in 466 cervices, a frequency of 1.9 percent. The lesion varies considerably in frequency as revealed by Patel and Bhagavan (314), who found only 3 in 2,500 hysterectomy specimens. At least 50 examples of this lesion have been described (98,314). Patients range from 22 to 73 years of age. Typically, blue nevi appear as ill-defined lesions in the lower endocervix, usually posteriorly, but they

have also been found in endocervical polyps. Most are incidental findings in biopsy, conization, or hysterectomy specimens (139)

Gross Findings. Blue nevi are blue to black, flat, and usually only 2 or 3 mm in greatest dimension, but lesions as large as 1.5 and 2.0 cm have been described (314). About 20 percent are multiple.

Microscopic Findings. The lesion is similar to blue nevi in the skin. It is composed of collections of elongated, wavy dendritic cells arranged individually and in clusters just below and parallel to the endocervical epithelium. Macrophages accompany the dendritic cells in the stroma. The cytoplasm of the nevus cells is filled with fine, brown, nonrefractile melanin pigment that stains green with the Lillie melanin stain and black with the Grimelius and Fontana-Masson stains. The granules fail to react with Prussian blue and colloidal iron stains, thus excluding hemosiderosis. Immunostains for S-100 protein are usually positive. Ultrastructural examination confirms the dendritic nature of the elongated cytoplasmic processes and demonstrates electron-dense membrane-bound melanin granules and premelanosomes.

Differential Diagnosis. The main lesions to consider in the differential diagnosis are melanosis and malignant melanoma. Melanosis is composed of benign, pigmented melanocytes in the basal layer of the epithelium and may be confused with blue nevus. At least five examples have been reported in the ectocervix (28). The lesion is flat and dark, and only 1 to 3 mm in diameter. The melanocytes are confined to the basal layer, but unlike melanosis in the skin, they are not accompanied by thickening of the epithelium. The melanocytes are usually densely pigmented and dendritic, but unlike blue nevus, do not involve the stroma.

Malignant melanoma has junctional change and stromal infiltration by malignant cells. Hemosiderosis is similar microscopically, but the hemosiderin granules are coarser, more refractile, and stain for iron. Furthermore, they do not stain with a Fontana-Masson stain and are found in macrophages rather than in dendritic spindle cells.

The pathologic effects of Monsel solution, a ferric subsulfate compound, which is frequently used as a hemostatic agent after cervical biopsy, may be confused with blue nevus. Monsel solution promotes the formation of hemosiderin deposition, but unlike blue nevus, does not contain dendritic cells (94). Accordingly, Monsel deposits stain for iron with Prussian blue (Terry Barrett, personal communication, year?).

Malignant Melanoma

Forty-four primary *malignant melanomas* of the cervix have been reported (70). They are one fifth as common as primary melanoma of the vagina and vulva. Melanoma of the cervix occurs in women ranging in age from 26 to 74 years, who present with vaginal bleeding or discharge, often of short duration (152,279,280). About half of melanomas of the cervix involve the vagina (stage II) when discovered (279,280).

Typically, melanomas appear as ulcerated, grayish blue or black protuberances or nodules. The tumor has a varied microscopic appearance, similar to cutaneous melanomas and those arising in the vagina (figs. 5-135, 5-136). Small cell and spindle cell variants are common. Even in the usual epithelioid cell type, areas of small, undifferentiated cells may occur. Junctional activity has been identified in less than half of the cases (280,350). Melanin pigment may be evident in H&E-stained slides.

The differential diagnosis includes melanoma metastatic to the cervix. Most of these are primary in the vagina or vulvar skin. Metastatic melanoma, in contrast to primary melanoma, usually lacks junctional change. Melanoma-specific HMB45, Melan-A, and S-100 protein immunostains help distinguish melanoma from carcinoma, although a few poorly differentiated carcinomas are S-100 protein positive. Immunoreactions for keratin are negative in melanoma.

Patients with melanoma of the cervix have a poor prognosis. In summarizing melanomas of the cervix, Mordel et al. (279) found a 5-year survival rate of 40 percent for patients with stage I disease, but only 14 percent for those with higher stages. Most patients who die of tumor do so within 1 year of diagnosis. The most common and earliest site of spread from melanoma of the cervix is to the vagina by direct extension and metastasis. A successful treatment has not yet been found.

Glomus Tumor

A few examples of *glomus tumor* of the cervix that presented as incidental findings have been

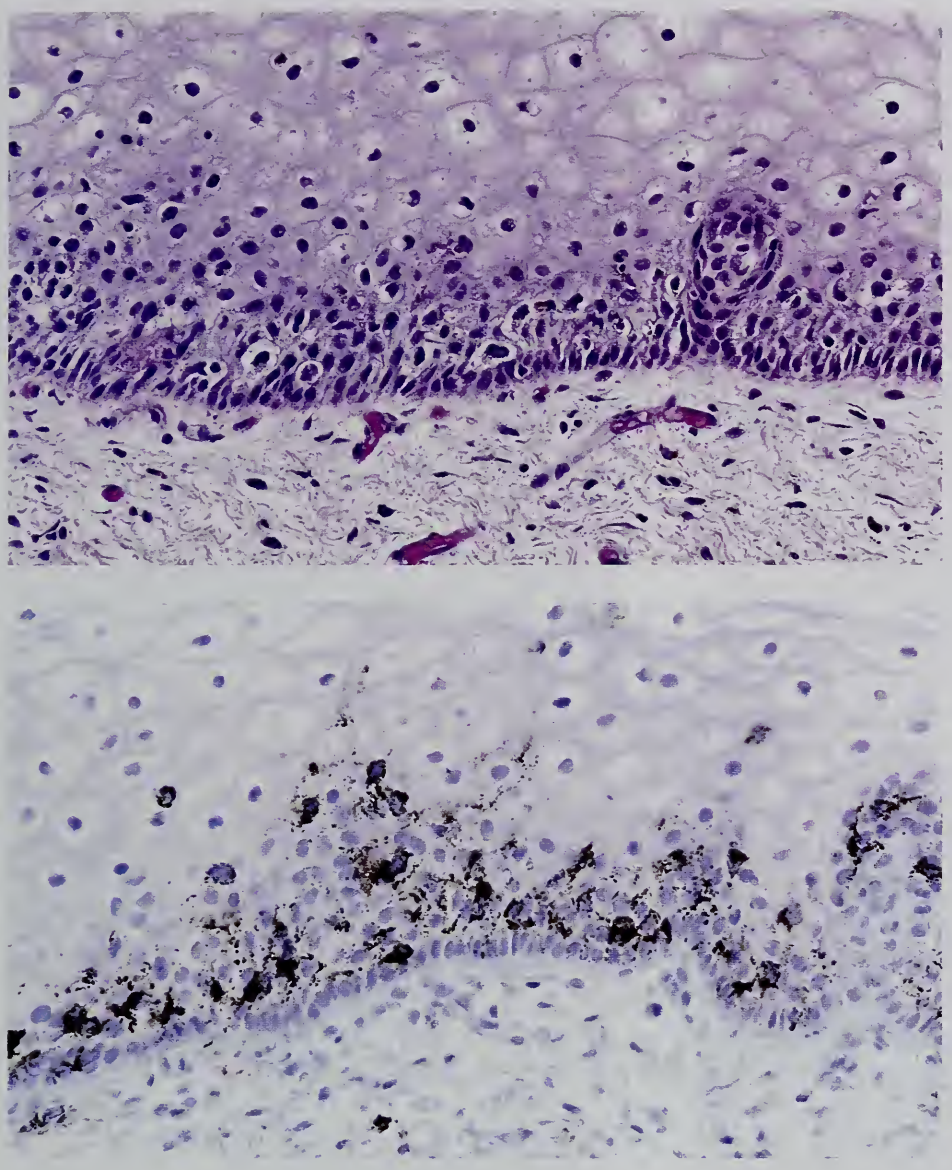


Figure 5-135

MELANOMA IN SITU

Top: Atypical melanocytes are present in the parabasal cell layer.

Bottom: Immunostain for HMB45 highlights more atypical melanocytes than are evident in the hematoxylin and eosin (H&E)-stained section.

reported (11). The tumors are less than 1 cm and are located deep in the cervical stroma. They have the features of glomus tumors found in other sites and are immunoreactive for smooth muscle actin and muscle-specific actin.

Lymphoma and Leukemia

Definition. *Lymphoma* and *leukemia* are malignant lymphoproliferative and hematopoietic neoplasms, respectively, that may be primary or secondary.

General Features. Lymphoma and rarely leukemia may become manifest initially in the cervix (62,160,221,253,417). More often, hematolymphoid disorders involve the cervix secondarily in the course of systemic spread. In reports, a distinction is seldom made between involvement of the cervix and involvement of the corpus. The cervix is more often affected as an initial manifestation of lymphoma than the uterine corpus or vagina (62,160). At autopsy, 2 to 9 percent of women with lymphoma have involvement of the uterus, about half of which is in the cervix (62).

Clinical Features. The median age of women with lymphoma or leukemia is slightly over 40 years of age, with the age ranging from the third to ninth decade of life (62,160). More than 75 percent of patients present with a mass, 50 percent with vaginal bleeding, and 33 percent have vaginal discharge. When the cervix is the initial site of disease, some patients also have anemia, lymphadenopathy, splenomegaly, or other signs of lymphoma at the time of diagnosis.

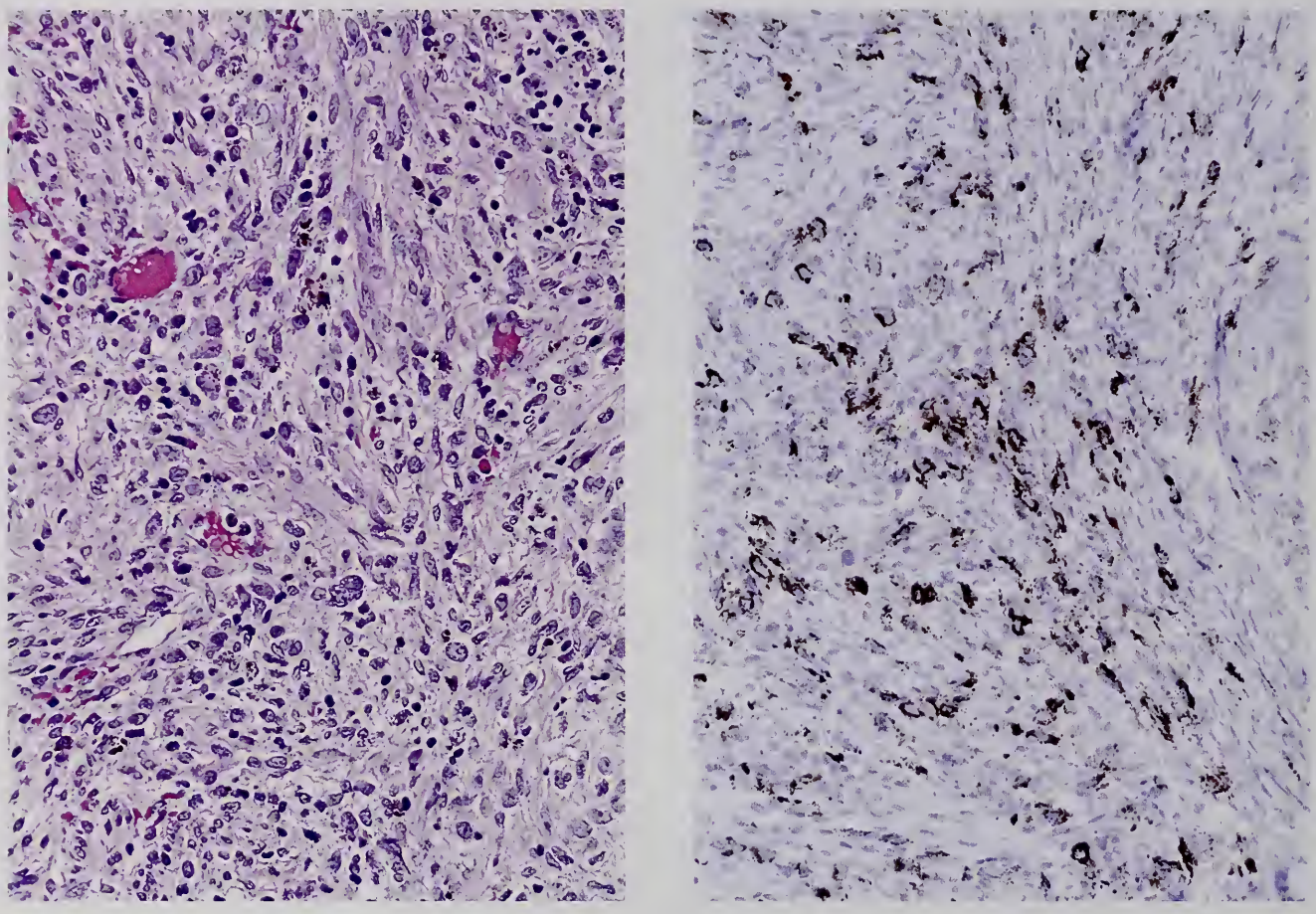


Figure 5-136

MELANOMA

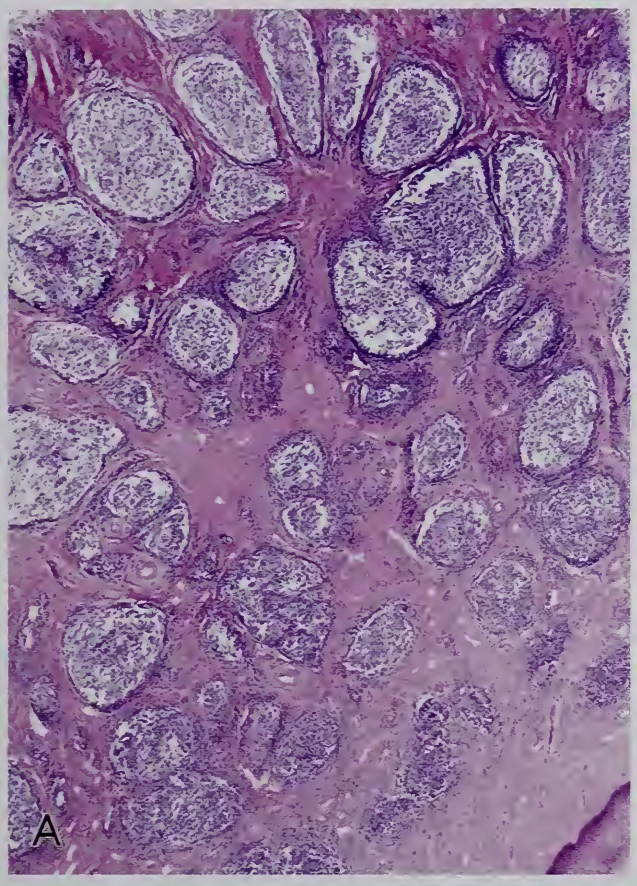
Left: The invasive component consists of atypical spindle cells, which are admixed with inflammatory cells. Right: Expression of HMB45 confirms the diagnosis of melanoma.

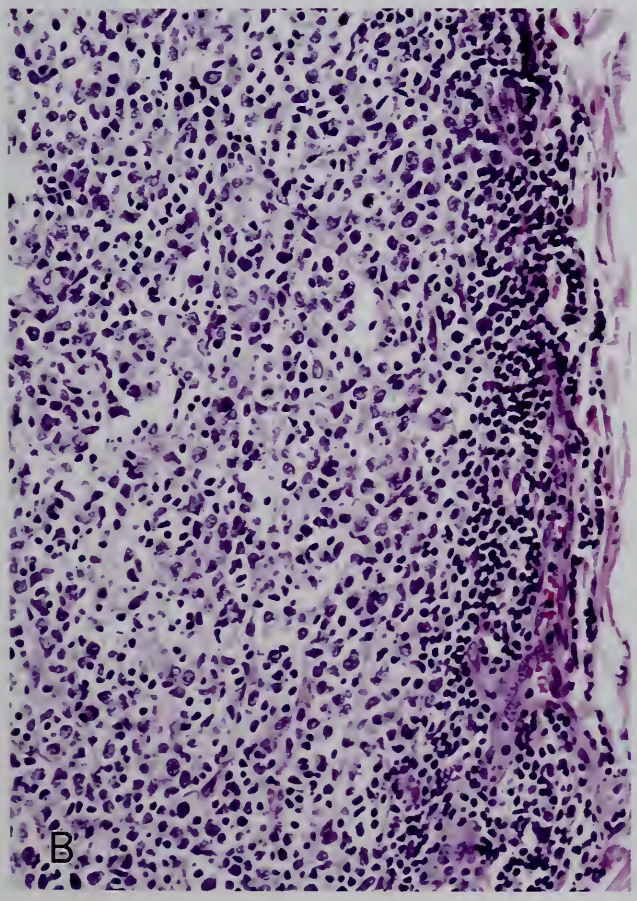
The duration of symptoms varies from 1 to 4 months. In about half the patients, the disease is stage II or more by FIGO criteria, being beyond the cervix and extending to the pelvic wall or lower third of the vagina. Cervical cytology smears are usually negative (221,253).

Gross Findings. Lymphoma most commonly appears as a diffuse or multinodular enlargement of the cervix, without epithelial abnormalities. The next most common presentation is as a polypoid endocervical mass protruding through the cervical os. Least commonly, the cervix has a granular, ragged or reddened surface as a result of ulceration by the tumor. Hodgkin disease, the rarest form of lymphoma of the cervix, tends to be firmer than the typical fish-flesh consistency of non-Hodgkin lymphoma (18). Granulocytic infiltrates may be green when freshly cut, giving rise to the term "chloroma."

Microscopic Findings. Lymphoma and leukemic infiltration produce two distinct low-power patterns, one infiltrating and one nodular (fig. 5-137). Follicular lymphomas and diffuse large B-cell lymphomas are the most common subtypes in the cervix. Myeloid leukemia, in particular, infiltrates the intrinsic structures of the cervix without destroying the landmarks. Infiltration of vessel walls is characteristic. Extensive sclerosis occurs in some infiltrates and crush artifact is common.

Immunohistochemical Findings. The immunostains recommended for a workup of lymphoma include leukocyte common antigen (LCA), investigation of monoclonality of immunoglobulin (light chain restriction), CD20 for B cells, CD3 for T cells, and CD30 and CD15 for Hodgkin disease. Cytokeratin stains are negative in lymphoma and leukemia. A chloroacetate esterase stain and immunostains





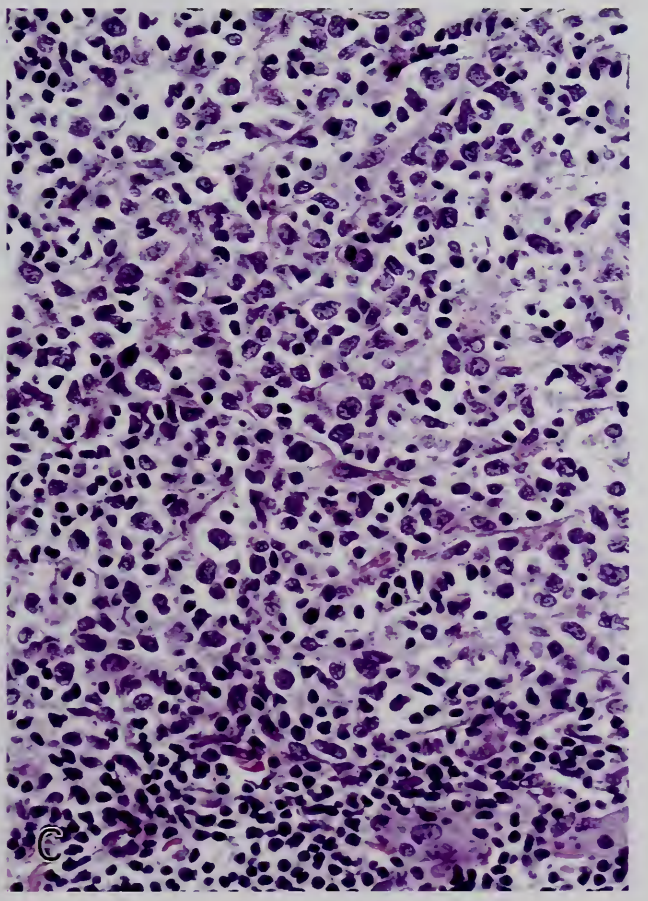


Figure 5-137

LYMPHOMA

A: The tumor has a follicular pattern and extends deep into the cervical stroma.

B: Follicles are composed of small and large lymphoid cells.

C: A neoplastic follicle contains small and large lymphoid cells and lacks other mixed inflammatory cells, including tingible body macrophages.

for myeloperoxidase or lysozyme for granulocytes and monocytes help identify myeloid infiltrates; CD34 identifies leukemic blasts.

Differential Diagnosis. Lymphoma-like lesion (pseudolymphoma), follicular cervicitis, small cell undifferentiated carcinoma, and metastatic carcinomas are the main considerations in the differential diagnosis (fig. 5-138). The cervix often is the site of an intense inflammatory response, but lymphoma-like lesions have a mixed cell infiltrate, indicative of a reactive process, and may form germinal centers. Lymphoma-like lesion is seldom, if ever, monomorphic. It is more superficial than lymphoma, is usually ulcerated, and almost always contains niduses of polymorphonuclear leukocytes and plasma cells. As in other organs, some lesions classified as "pseudolymphoma" are now recognized as mucosa-associated lymphoid tissue (MALT) lymphoma (318). Lymphoma, in contrast, forms a larger lesion that deeply invades the stroma, often with associated sclerosis, deep perivascular infiltration, and a monomorphic cell population (436). A thin, uninvolved, subepithelial stromal layer is almost always present in cases of lymphoma. Immunostains may be needed to confirm the monoclonal nature of the infiltrate and thereby distinguish lymphoma from lymphoma-like lesions that are polyclonal.

A leukemic infiltrate may be difficult to distinguish from a poorly differentiated carcinoma. Leukemic cells do not have the cohesive quality resulting from cell membrane adherence that characterizes carcinoma. LCA positivity, when present, distinguishes a lymphoma or leukemia from primary or metastatic small cell carcinoma. A positive immunochemical stain for keratin identifies most carcinomas, but if the stain is negative, neuroendocrine markers may be positive in small cell carcinoma. Imprint preparations and cytologic smears are useful in distinguishing lymphoma and leukemic infiltrates from carcinoma in which the cells are adherent, clustered, and display epithelial characteristics, unlike the cells of lymphoma and leukemia.

Treatment and Prognosis. The actuarial 5-year survival rate for patients with stage I lymphoma of the cervix is more than 75 percent (160,221,391). In one study, none of the 12 patients with stage I lymphoma of the cervix or vagina who received definitive initial local treatment in the form of surgical excision or radiation therapy had relapse of their tumor (160). In another study, 4 of 6 patients with extranodal lymphoma had no evidence of disease after 1 year or more of follow-up (62). Myeloid sarcoma presenting in the cervix may take 2 years or more to become evident systemically (62,361). Radiation therapy is recommended for lymphoma, with combination chemotherapy advocated for patients with systemic disease (221).

GERM CELL TUMORS

Mature Teratoma (Dermoid Cyst)

Teratomas of the cervix are composed of mature elements, including squamous epithelium organized as skin with sebaceous glands and hair overlying fat. Bone, cartilage, mature lymphoid tissue, choroid plexus, and ganglion cell differentiation also accompany the epidermal differentiation. Teratomas contain more than ectodermal derivatives, distinguishing them from epidermal metaplasia. All have been benign. Teratomas of the uterus are uncommon; most are primary polypoid lesions of the cervix, when the origin is known (157,211).

Yolk Sac Tumor

Yolk sac tumor occurs as a primary tumor of the cervix, just as it does in the vagina (81,442). Although most yolk sac tumors arising in the vagina do not involve the cervix, some involve both areas at presentation. Often, the primary site is not clearly defined, but approximately 10 to 15 percent of yolk sac tumors of the lower genital tract originate in the cervix and the majority arise in the vagina. The tumor develops in young children, usually from 14 to 27 months of age, and produces a blood-tinged vaginal discharge. Alpha-fetoprotein serum levels are elevated.

Grossly, yolk sac tumor is soft, friable, pedunculated or polypoid, and partially eroded. Microscopically, they are similar to those in the vagina. Reticular, solid, and festoon patterns of yolk sac tumor are common, whereas the polyvesicular and hepatoid patterns have not been described. Schiller-Duval bodies are common in most neoplasms. Although early reports described a dismal outlook, modern combination chemotherapy and surgery offer a reasonable chance of cure (259).

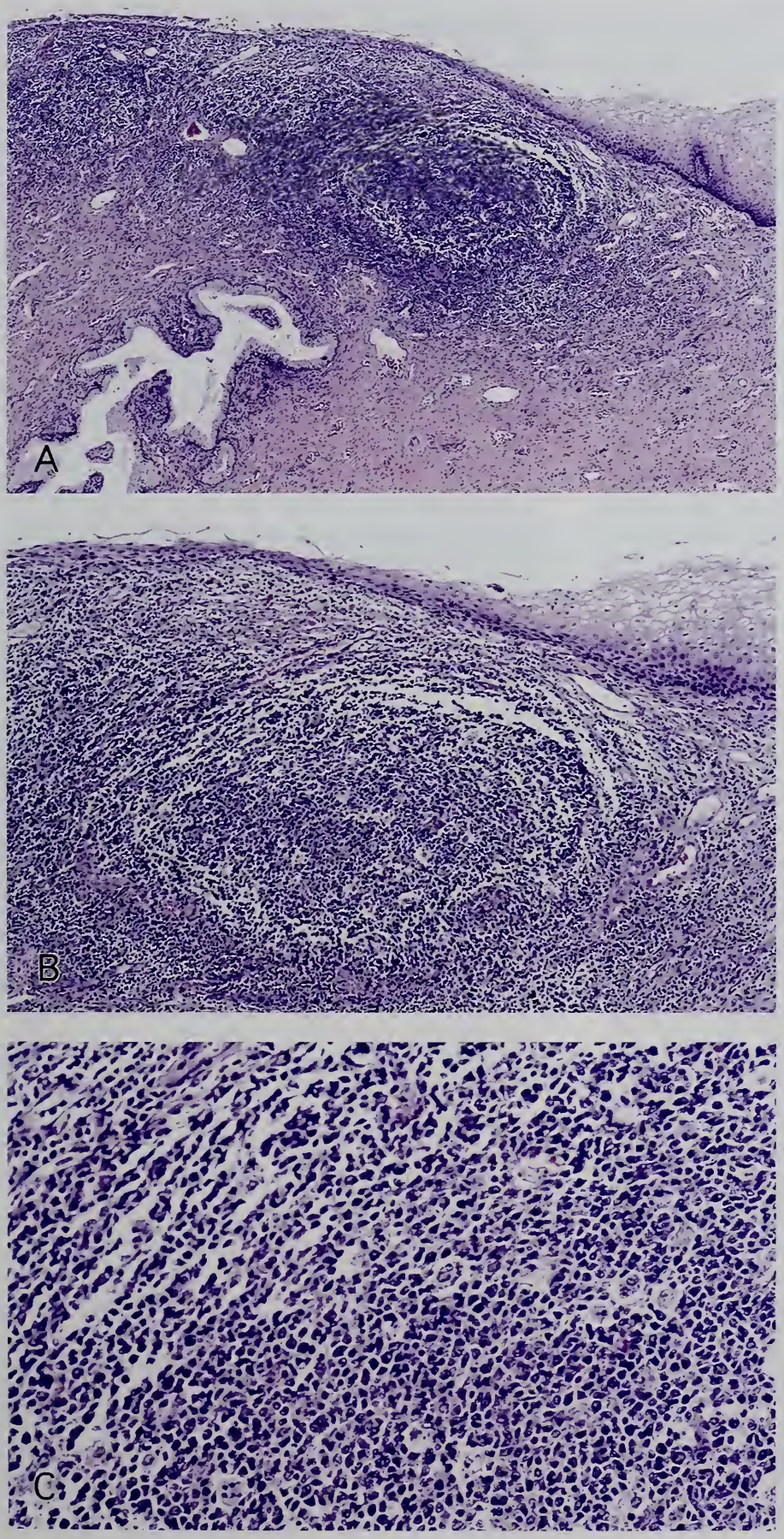


Figure 5-138

FOLLICULAR CERVICITIS

A: The lesion is characterized by a plaque-like chronic inflammatory infiltrate, with one lymphoid follicle containing a germinal center.

B: A lymphoid follicle with germinal center is present in the superficial stroma beneath attenuated cervical mucosa.

C: A follicle contains small lymphocytes and tingible body macrophages.

SECONDARY TUMORS

About half of *secondary tumors* of the cervix result from direct extension from an endometrial primary tumor (7). Poorly differentiated adenocarcinoma of the endometrium is particularly likely to invade the cervix directly. Distinction from a primary carcinoma of the cervix extending to the endometrium may be difficult. A diagnosis of a primary endometrial carcinoma is made if the endometrial lesion is larger, if the cervical lesion is superficial, and if the microscopic pattern is consistent with an endometrial origin. The presence of coexistent endometrial hyperplasia supports an endometrial origin, whereas the presence of SIL or AIS of the cervix supports a primary cervical neoplasm. The clinical presentation usually provides clues as to the primary site, but at times, examination of the hysterectomy specimen is needed (see Endocervical Adenocarcinoma).

Cervical involvement by endometrial endometrioid carcinomas displaying deceptive patterns of spread and altered morphology in some cases, simulating independent cervical tumors or even benign lesions, have been reported (396). The cervical tumors were composed of tubular glands often containing eosinophilic secretions in their lumens, simulating mesonephric lesions, and some elicited little or no stromal response, simulating benign lesions. The similar immunoprofiles and continuity of the cervical and uterine corpus tumors in most of the cases support interpretation of the cervical involvement as secondary extension of the endometrial carcinoma and not an independent cervical neoplasm.

Metastasis from extragenital tumors involves the ovary and vagina much more often than the cervix. In an autopsy study of 1,000 patients who died of carcinoma (7), metastases to the cervix were found in only 0.3 percent. Breast, stomach, and colon carcinomas are the most frequent extragenital tumors to metastasize to the cervix, with occasional metastases from lung, pancreas, bladder, liver, kidney, and gallbladder (7,242,424).

Carcinoma of the breast is the most common extragenital tumor to metastasize to the cervix. Of breast carcinomas metastatic to the cervix, 80 percent metastasize within 1 year of treatment of the breast tumor (432). Most of the other metastases were discovered at the time of diagnosis of the breast carcinoma, and in only 1 patient of 24 reported, was the metastasis to the cervix the initial manifestation of the disease. The mean survival period after identification of the metastatic tumor is only 1 year.

More than 30 cases of carcinoma of the stomach metastatic to the cervix have been reported (fig. 5-139) (239,263), and about one third of them present in the cervix with suspicious or malignant cells in cervical smears (263). Of the carcinomas of the lung that have metastasized to the cervix, most have been of the small cell variety. More than 20 cases of carcinoma of the colon or rectum have metastasized to the cervix (424), but in only 1 case was cervical involvement the initial presentation of the carcinoma.

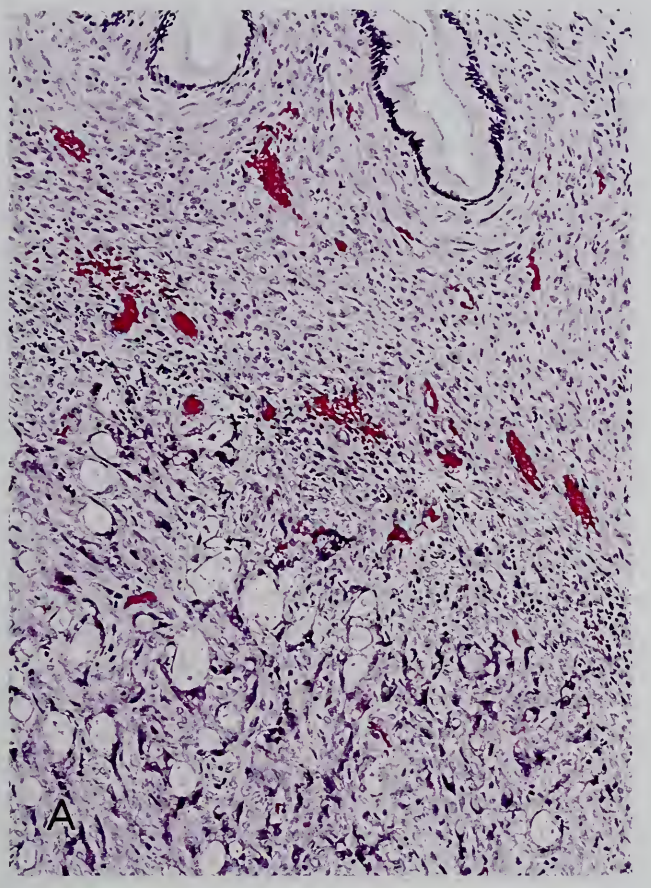
Regardless of the primary site, nearly 90 percent of women with metastasis to the cervix have evidence of widespread disease (432). The most common symptom of metastasis to the cervix is vaginal bleeding, occurring in 75 percent of patients.

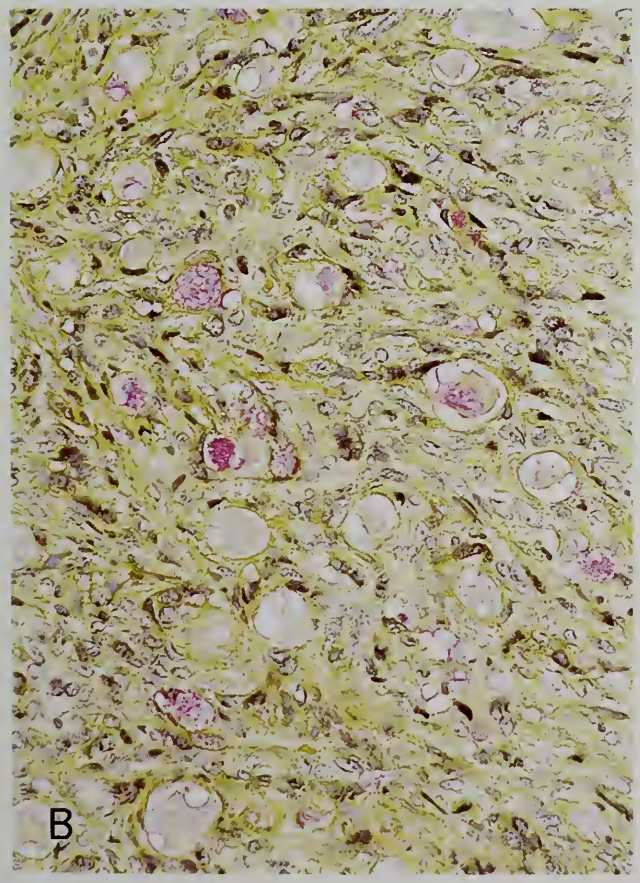
Grossly, the cervix usually appears normal, but it may reveal a minor eccentric thickening, small erosions, or slight irregularity of the mucosal surface. Microscopically, multiple nodular subepithelial infiltrates are evident. Most metastases are poorly differentiated, infiltrating around endocervical glands and involving lymphatic spaces. Features that suggest metastasis are the absence of an in situ component and extensive lymphatic permeation in otherwise small superficial lesions. Immunostains for epithelial markers are often helpful in excluding a lymphoma or leukemic infiltrate.

TUMOR-LIKE LESIONS

Epidermal Metaplasia

Epidermis, sebaceous glands, and hair follicles, alone or in combination, may occur in the cervix. Sebaceous glands alone have been described in eight cases (147). The origin of skin constituents in the cervix is controversial. Most investigators favor *mesodermal metaplasia*, but others favor a *heterotopia*. Epidermal differentiation in the form of sebaceous and eccrine glands and hair follicles has been found within a squamous cell carcinoma of the cervix (147). This lesion should be distinguished from a mature teratoma, which also occurs in the cervix.





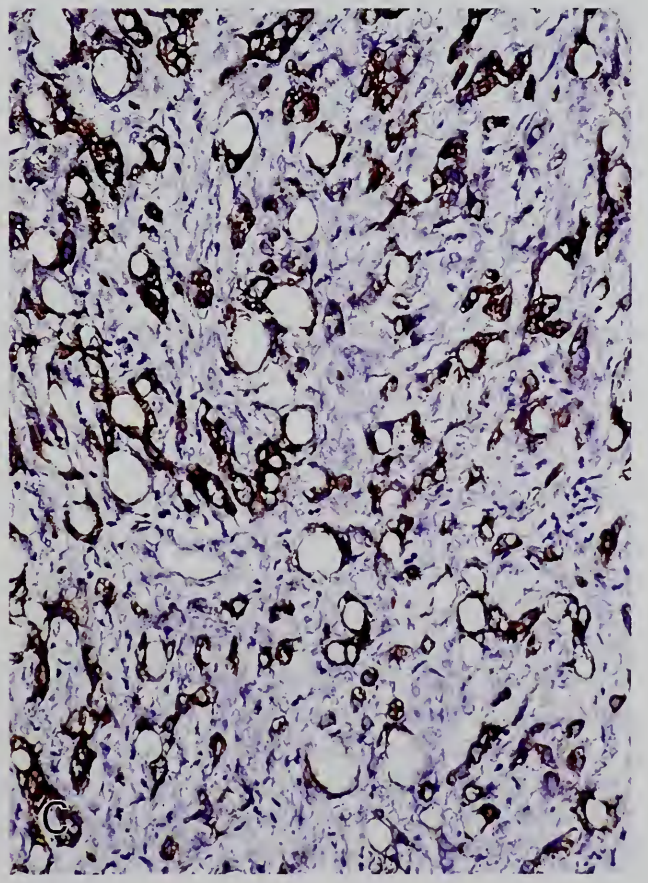


Figure 5-139

METASTATIC ADENOCARCINOMA

A: The endocervical stroma contains adenocarcinoma exhibiting signet ring cell differentiation. This suggests metastatic adenocarcinoma of gastrointestinal tract origin rather than a primary cervical carcinoma.

B: Mucicarmine stain demonstrates intracellular mucin vacuoles.

C: The tumor exhibits diffuse expression of CK20. Combined with morphology, this pattern is most consistent with metastatic adenocarcinoma of gastrointestinal tract origin (stomach or appendix).

Lymphoma-Like Lesion (Pseudolymphoma)

Inflammatory lesions in the cervix are seldom so extensive that they are confused with lymphoma. Rare lesions, however, reach a size and uniformity of cell type that can be confused with lymphoma. These have been designated *lymphoma-like lesion*, or *pseudolymphoma* (436). Patients range in age from 19 to 65 years, with an average of 35 years. Symptoms include vaginal bleeding, postcoital bleeding, discharge, and fever. Pelvic examination discloses a normal-appearing cervix in some patients, but in most, it is abnormal and bleeds easily when touched.

Lymphoma-like lesions are soft, nodular, superficial, and focally eroded. Microscopically, large clusters or diffuse sheets of large lymphoid cells admixed with mature lymphocytes, plasma cells, and neutrophils are seen. The infiltrate is band-like and superficial, usually only 3 mm in depth. The presence of macrophages and germinal centers supports a benign diagnosis. The infiltrate seldom extends below the level of the endocervical glands, a helpful point in distinguishing it from lymphoma.

MALT lymphoma of the cervix, although very rare, may mimic a lymphoma-like lesion because it may be polymorphous and have residual follicles. Immunoglobulin immunostains identify polyclonality, a useful feature in distinguishing lymphoma-like lesion from lymphoma. Rosai-Dorfman disease, a condition in which large histiocytes contain engulfed lymphocytes, has been described, as have histiocytosis and malakoplakia of the cervix. These seldom have the monomorphous appearance of lymphoma and the microscopic pattern is dominated by histiocytes rather than lymphocytes, as in lymphoma-like lesion (282).

Decidual Nodule

Decidual nodules occur just beneath the epithelium in the cervix during pregnancy. They seldom exceed 3 or 4 mm in diameter. Decidual cells are uniform in size, with abundant pale granular cytoplasm and a well-defined cell membrane. A decidual nodule may be confused with nonkeratinizing squamous cell carcinoma or a placental-site nodule (see below). The decidual cells, however, have no continuity with the surface epithelium and are not associated with an intraepithelial neoplasm. They have uniform bland nuclei, differing from the more pleomorphic nuclei of the placental-site nodule and the nuclei of nonkeratinizing squamous cell carcinoma, which have coarsely clumped chromatin. Decidual cells also have no mitotic figures. An immunohistochemical stain for keratin is negative in decidual cells, whereas it is positive in squamous cell carcinoma and placental-site nodule.

Placental-Site Nodule

Early implantation sites are small and usually not visible grossly. Approximately 50 percent occur in the cervix, with the remainder in the endometrium. Rare cases have been described in the fallopian tube (369). The lesion in the cervix is usually an incidental finding or detected in a cervical biopsy or cone biopsy done for evaluation of an abnormal Pap smear.

The *placental-site nodule* is located immediately beneath the epithelial surface and appears as a well-defined nodular hyalinized lesion composed of intermediate trophoblast showing cytoplasmic vacuolization and occasional inflammatory cells. The intermediate trophoblastic cells are mainly mononucleate, but some are multinucleate. Confusion with early squamous cell carcinoma is possible. Placental-site nodules, however, lack significant atypia and only rarely contain mitotic figures. In addition, the cells are usually positive for CK18 and inhibin while squamous cell carcinoma is negative for both markers.

Amputation (Traumatic) Neuroma

An *amputation (traumatic) neuroma* occurs in the cervix as a rare complication of conization (30). An irregular, firm, gray area of up to 2 mm forms in the region of the conization margin or scar. Microscopically, numerous haphazardly arranged tangles of nerves are evident within a scar composed of mature collagen and entrapped smooth muscle fibers. An immunohistochemical stain for S-100 protein confirms the presence of nerve fibers within the collagen.

Postoperative Spindle Cell Nodule

Postoperative spindle cell nodule may develop in the cervix after trauma, such as biopsy or curettage (206). The lesion develops more commonly in the vulva and vagina and only occasionally recurs after excision (325). A history of recent

trauma or surgery is helpful in establishing the diagnosis. The lesion resembles nodular fasciitis, being composed of loose, actively proliferating spindle cells that may appear to infiltrate at the periphery. The cells form bundles and fascicles, often separated by edema. A delicate network of capillaries is present within the lesion, and neutrophils and erythrocytes are often prominent, producing a resemblance to granulation tissue. The nuclei are oval to spindle shaped, but vary in size. Some are swollen or mildly hyperchromatic. Mitotic figures are common but abnormal mitotic figures are absent.

Glial Polyp

Glial tissue in the cervix is very rare: 33 cases have been reported (248,339,437). Glial tissue containing bland astrocytes typically occurs as a discrete, small polypoid lesion in the endocervix. In one instance, the endometrium and the endocervix were extensively infiltrated by soft white polypoid tissue 10 cm in extent (437). Most *glial polyps* are small and confined to the endocervix.

Microscopic examination shows glial tissue of low to moderate cellularity surrounding nearby endocervical glands and invading the stroma at the margin. Within the glia, astrocytes are evenly spaced, multipolar with long radiating processes, and without atypia. Interwoven fine fibrillary processes are present. Immunostains for glial acidic fibrillary protein (GFAP) may be positive in the cytoplasm of the astrocytic cells as well as in the glial stroma. All glial polyps have been benign, although several recurred as late as 5 years after initial excision (339).

Three origins have been proposed for the presence of glia in the cervix. First, fetal brain tissue may be implanted at the time of curettage or abortion and persist as a graft. Patients with a glial polyp, like those with heterotopic cartilage, are commonly of reproductive age and have a history of abortion or instrumentation, consistent with an origin of the glia or cartilage from retained fetal products (343). In some cases, the glia has been accompanied by choroid plexus, cartilage, bone, and even fatty tissue, further supporting the view that the lesion is a result of fetal implantation (248). The finding of bulky glial differentiation within the endometrium in a young virgin implies a second origin from monodermal overgrowth of a teratoma. The third origin suggested is mesodermal metaplasia. This is an unlikely possibility for the origin of glial polyps, however, since there is no underlying neoplasm or other lesion to give rise to the glia via metaplastic transformation. Mesodermal metaplasia to glia has been identified in several malignant mesodermal mixed tumors (126).

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6 TUMORS OF THE VAGINA

SQUAMOUS LESIONS

Squamous Papilloma

Squamous papilloma of the vagina is a benign papillary lesion similar in its gross and microscopic appearance to squamous papillomas involving the ectocervix and vulva (see chapters 5 and 7). In the vagina, squamous papillomas are only a few millimeters in greatest diameter, may be single but more often are multiple, and typically occur in clusters. They occur anywhere in the vagina, but characteristically are located around the hymenal ring, often merging with similar lesions in the vulvar vestibule. Multiple lesions are referred to as *squamous papillomatosis.*

As indicated in the previous chapter, squamous papillomas are not related to human papilloma virus (HPV) infection. HPV DNA has occasionally been reported in women with squamous papilloma (87,101) but because HPV DNA sequences are found in 10 to 20 percent of vaginal and vulvar scrapings from women without discernable lesions, the occasional presence of HPV DNA in squamous papillomas is probably coincidental.

Squamous papillomas may be difficult to distinguish from condylomas. In contrast to condylomas, squamous papillomas lack koilocytes and a complex arborizing architecture. Instead, they are composed of a single papillary frond with a central fibrovascular core (fig. 6-1).

Patients are usually asymptomatic. When lesions are extensive, and particularly when they involve the vulvar vestibule, they may produce burning or dyspareunia characterized by an abrasive sensation localized to the introitus. Lesions causing no symptoms require no treatment. Those associated with dyspareunia respond to ablative treatment with trichloroacetic acid or laser vaporization.

Condyloma Acuminatum

Vaginal condylomas are similar in their gross and microscopic appearance to condylomas arising on the ectocervix and vulva and are described in detail in the cervix and vulva chapters.

Transitional Metaplasia

Transitional metaplasia is composed of basal and parabasal cells with ovoid nuclei resembling transitional epithelium. It is important to distinguish transitional metaplasia from high-grade vaginal intraepithelial lesions (see Squamous

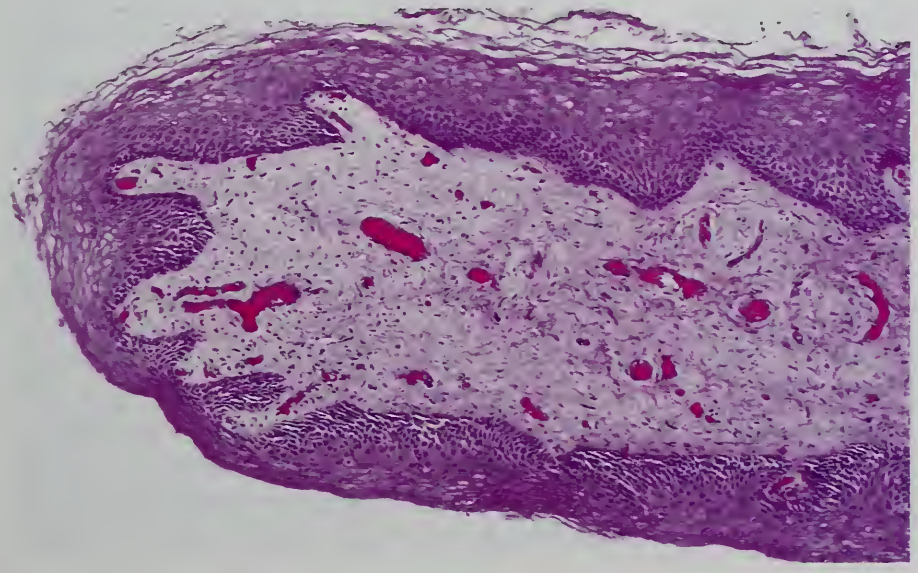


Figure 6-1

SQUAMOUS PAPILLOMA

The papillary structure is lined by squamous epithelium lacking verruciform growth and contains a fibrovascular core.

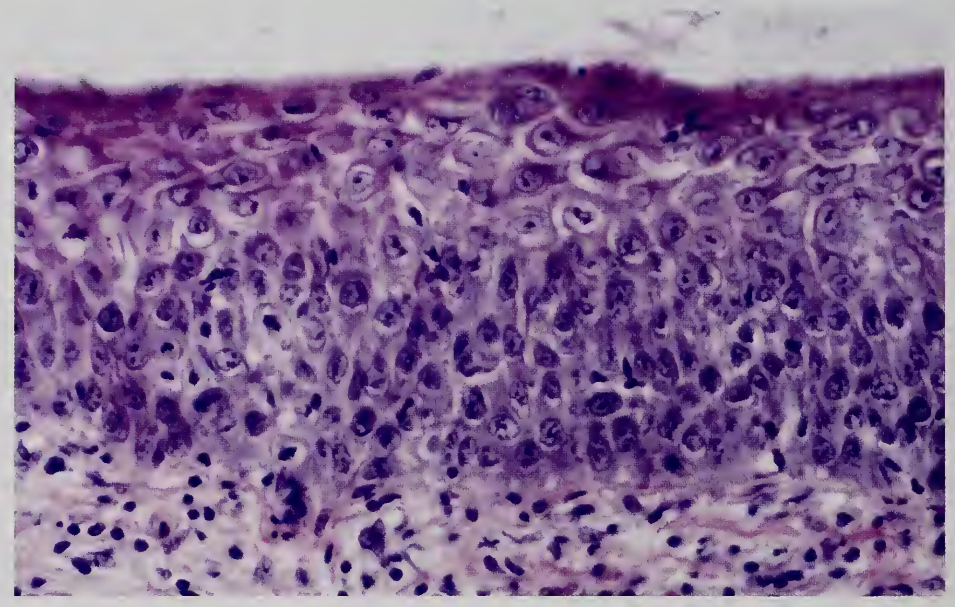


Figure 6-2

SQUAMOUS ATYPIA

Parabasal layers contain cells with enlarged vesicular nuclei with small nucleoli. Inflammatory cells are present in the superficial stroma and within the epithelium.

Intraepithelial Lesions). In transitional metaplasia, the cells are uniform, lack disorganization, and have bland nuclei. There is little, if any, mitotic activity. A counterpart of this lesion occurs in the cervix.

Squamous Atypia

Squamous atypia is similar to its counterpart in the cervix. It is characterized by a generally uniform population of cells with nuclear enlargement and prominent nucleoli. The cells are not crowded and retain an orderly pattern of maturation. Typically there are marked acute and chronic inflammation in the stroma and leukocytes in the epithelium (fig. 6-2). The latter help distinguish squamous atypia from vaginal intraepithelial neoplasia (VaIN) because it is unusual to see leukocytes within the epithelium of VaIN, although there often is an inflammatory infiltrate in the stroma.

Squamous Intraepithelial Lesions

Definition. *Squamous intraepithelial lesions* (SIL) are proliferative lesions with abnormal maturation, nuclear enlargement, and atypia. The atypia is characterized by pleomorphism, coarse chromatin clumping, and irregular nuclear contours. In the past these lesions have been termed *dysplasia, carcinoma in situ* (CIS), and *vaginal intraepithelial neoplasia* (VaIN). In the Bethesda System, vaginal cytologic smears showing VaIN 1 are designated *low-grade SIL* (LSIL) and VaIN 2 and 3 are designated *high-grade SIL* (HSIL).

Although most authorities now prefer a two-tier nomenclature for histology, as in the vulva, there is disagreement as to whether SIL should be termed LSIL/HSIL or condyloma/HSIL. A recent study (129) has shown that low-grade lesions contain both low- and high-risk HPV, similar to the distribution of HPV in LSIL of the cervix. In this text, we use LSIL/HSIL for vaginal, vulvar, and cervical lesions. Since most reports in the literature had, until recently, used the VaIN terminology, when these studies are cited, VaIN or dysplasia/CIS will be used.

General Features. Intraepithelial lesions of the vagina have been recognized relatively recently, probably because of a heightened awareness of their existence. Most are not apparent on clinical examination but are diagnosed by cytologic smears. The average age-adjusted incidence rate in the United States is 0.20/100,000 for white and 0.31/100,000 for black women (47). The ratio of vaginal to cervical intraepithelial lesions is 1 to 23 (61). The mean age of women with VaIN 3 (HSIL) is 53 years, approximately 10 years older than women with cervical intraepithelial neoplasia (CIN) 3 (58). Although vaginal lesions are almost invariably diagnosed after the cervical neoplasia is treated, this may not reflect the natural history of the disease but may be an artifact of cytology screening; i.e., in women who have not had a hysterectomy, smears are generally obtained from the cervix. Only after a hysterectomy for malignant or benign disease are smears taken from the vagina,

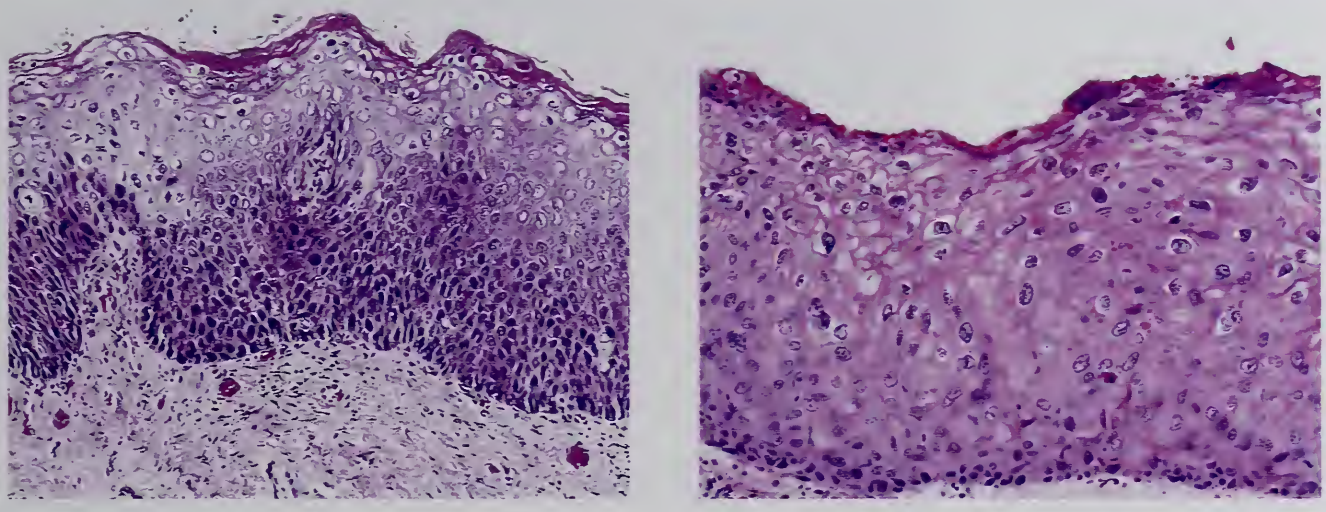


Figure 6-3

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION (VAGINAL INTRAEPITHELIAL NEOPLASIA 1 [VAIN 1])

Left: The flat lesion exhibits a widened parabasal zone, surface maturation with koilocytosis, and a slightly verruciform surface contour.

Right: The flat lesion shows maturation but the nuclei in the intermediate and superficial zones are mildly enlarged. Some cells with these abnormal nuclei display cytoplasmic clearing (koilocytosis).

and therefore, preexisting VaIN (SIL) may have been overlooked earlier.

VaIN 3 (HSIL) usually occurs in the upper third of the vagina and is multifocal or diffuse in nearly half the cases (7,68,117). One third of the patients have a history of prior CIN 3, sometimes as long as 22 years earlier. In addition, CIN coexists with VaIN in 10 to 20 percent of the cases (7,61,68,117). It has been suggested that the multicentric distribution of preinvasive and invasive squamous cell carcinomas in the lower genital tract is related to a common carcinogenic stimulus (73). This "field-effect" theory attempts to account for the development of multiple sequential or simultaneous carcinomas involving tissue derived from a shared anlage. The demonstration of HPV DNA sequences in cervical, vaginal, and vulvar neoplasms is consistent with this view. However, a recent study of multiple metachronous lower genital tract (vaginal and vulvar) dysplasias in women with a prior history of cervical dysplasia or carcinoma demonstrated identical HPV DNA integration sites in all lesions in each patient, indicating that high-grade dysplastic lesions of the lower genital tract may emerge as monoclonal lesions from a transformed cell population derived from the cervix (140). Another cause of VaIN is radiation exposure because a prior history of pelvic irradiation for benign uterine disease has been reported in most series (7,61,68,117). It is possible that HPV and radiation are synergistic in some cases.

Gross Findings. Like its cervical counterpart, SILs of the vagina are best appreciated by colposcopic examination after the application of 3 to 5 percent acetic acid. Colposcopic examination reveals well-circumscribed, white, slightly elevated lesions with epithelial and vascular patterns similar to those of CIN.

Microscopic Findings. SIL in the vagina is similar to SIL in the cervix, and the criteria for grading intraepithelial lesions are the same as for those of the cervix (figs. 6-3, 6-4).

Differential Diagnosis. Atrophy in older women, immature squamous metaplasia in women with adenosis, and reactive atypia are the lesions most commonly confused with SIL. Although both atrophy and immature squamous metaplasia display a high nuclear-cytoplasmic ratio, they lack nuclear atypia, which is the hallmark of SIL. The squamous (reactive) nuclear atypia is characterized by prominent nucleoli, retention of cell membranes and cellular polarity, and absence of marked cellular crowding and abnormal mitotic figures.

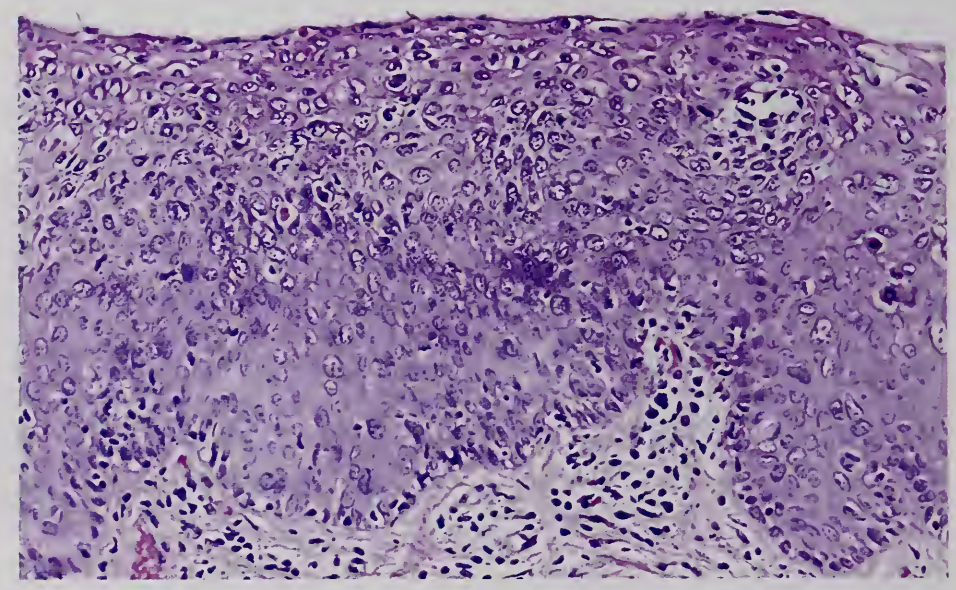
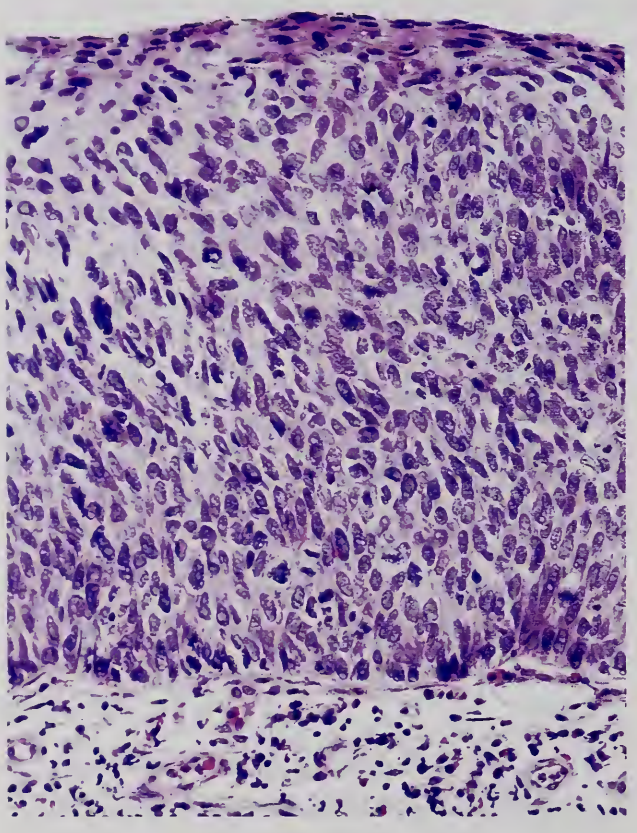


Figure 6-4

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (VAGINAL INTRAEPITHELIAL NEOPLASIA 2/3)

Right: Immature atypical parabasal cells fill the lower and middle thirds of the epithelium. The cells in the superficial layers have modest amounts of cytoplasm, indicating limited squamous maturation (VaIN 2).

Below: Immature atypical parabasal cells fill the entire epithelium and mitotic figures are evident in all layers (VaIN 3).



Because vaginal adenosis may be extensive in the diethylstilbestrol (DES)-exposed patient, complete replacement of the glands by immature squamous metaplasia may, under low magnification, resemble invasive squamous cell carcinoma. If attention is directed to the degree of cytologic atypia, the distinction between immature squamous metaplasia and invasive squamous cell carcinoma should not be difficult.

Treatment and Prognosis. SILs of the vagina are typically diagnosed in abnormal cytologic specimens in patients who have had a hysterectomy for cervical neoplasia or benign uterine disease. The presence of SIL in the vagina should also be considered in a patient with an intact uterus who has abnormal cytology that is inconsistent with the findings on cervical colposcopy, and in whom a cone biopsy shows no lesion. Progression to invasive vaginal carcinoma occurs in approximately 5 percent of patients and has been documented by serial biopsies showing changes from VaIN 1 (LSIL) through VaIN 2 and 3 (HSIL) to invasive cancer (117,124).

Similar lesions may follow radiation treatment for carcinoma of the cervix. These lesions are designated *postirradiation dysplasia* (93). The sooner they become evident, the more likely they are to be neoplastic. Those that develop within 3 years of radiation are associated with recurrent cervical carcinoma in 71 percent of patients, compared to 44 percent in women in whom dysplasia develops 3 years after radiation (147).

SIL may develop in women with adenosis who have been exposed to DES in utero. Vaginal adenosis in the DES-exposed woman corresponds somewhat to benign glandular epithelium of the cervical transformation zone in unexposed women. Some investigators regard vaginal adenosis in the DES-exposed woman as an extension of the cervical transformation zone from the cervix to the vagina. Because preinvasive and invasive squamous neoplasms of the cervix develop within the transformation

zone, there once was concern that squamous cell carcinoma would develop in a large proportion of the DES-exposed population because of the large transformation zone. The National Cooperative Diethylstilbestrol Adenosis (DESAD) Project reported an increased incidence of SIL in the cervix and vagina in the DES-exposed group compared with matched controls (112). The majority of these intraepithelial lesions, however, were low grade. The findings suggest that the DES-exposed patient, because of the large transformation zone, may be at a greater risk of HPV infection, which leads in turn to the development of SIL. At this point, an increase in the number of squamous cell carcinomas in the DES-exposed population has not been demonstrated.

Treatment of SIL is excisional biopsy for small lesions. Partial vaginectomy, laser vaporization (130), or intravaginal application of 5-fluorouracil cream (149) is reserved for more extensive lesions.

Squamous Cell Carcinoma

Definition. *Squamous cell carcinoma* is composed of malignant squamous cells and is often associated with squamous cell carcinomas of the cervix and vulva. It may be difficult to distinguish the site of origin of the tumor in cases involving more than one organ.

General Features. Invasive squamous cell carcinoma of the vagina accounts for 1 to 3 percent of all malignant tumors of the female genital tract. Cervical squamous cell carcinoma is 50 times more prevalent than vaginal squamous cell carcinoma (78). According to the International Federation of Gynecologists and Obstetricians (FIGO), a primary vaginal carcinoma must not involve the cervix; if there is cervical involvement, the tumor is considered a cervical carcinoma with extension to the vagina. In addition, in patients with a prior preinvasive or invasive cervical or vulvar carcinoma, a 5- to 10-year disease-free interval is considered necessary to exclude recurrent disease (96,103). Approximately 85 percent of recurrent cervical and vulvar cancers recur within the first 3 years after treatment, but it is usual for a vaginal tumor to develop 20 years after the treatment of a primary cervical carcinoma (2). From a practical standpoint, patients treated for cervical cancer must be carefully followed for the remainder of their lives. SIL and invasive squamous carcinoma of the vagina have many of the same risk factors as cervical cancer, including a strong relationship to HPV infection. In one study, women with vaginal cancer were more likely to have five or more lifetime sexual partners (22). In addition, they were more likely to have an early age at first sexual intercourse and to be smokers at diagnosis when compared with controls. Approximately 30 percent of all patients had been treated for an anogenital cancer, most often of the cervix.

Clinical Features. Patients range in age from the teens through the 80s, with a mean age of 64 years. They are approximately 10 years older than women with cervical carcinoma. Nearly 75 percent present with painless bleeding or urinary tract symptoms. Cytologic specimens are useful for detecting tumors in asymptomatic women.

Gross Findings. Vaginal carcinoma is commonly located in the upper third of the vagina, often involving the posterior wall. The tumors are ulcerative in half the cases, exophytic in a third, and annular and constricting in the remainder.

Microscopic Findings. Squamous cell carcinoma of the vagina displays a variety of histologic patterns, similar to those of cervical squamous cell carcinoma. The majority of the vaginal neoplasms are nonkeratinizing (35) and moderately differentiated (fig. 6-5) (104). There appears to be no correlation between the grade of the tumor and the prognosis (50).

Invasive squamous cell carcinomas are recognized occasionally at a "microinvasive" stage, characterized by tongues of tumor invading the stroma to a depth of 3 mm or less, as in microinvasive carcinoma of the cervix. When invasion is 3 mm or less measured from the basement membrane, metastasis is unlikely if lymphatic/vascular space invasion is not identified (97). There may be a subset of patients with minimal disease who can be treated conservatively, but additional cases must be studied before the term "microinvasive squamous carcinoma of the vagina" is justified as a distinct entity.

Staging. The FIGO and TNM staging systems for vaginal carcinoma are shown in Table 6-1.

Treatment and Prognosis. Squamous cell carcinomas spread by direct extension into the bladder, rectum, broad ligament, and rectovaginal septum. They also invade lymphatic and blood vessels, metastasizing to regional lymph

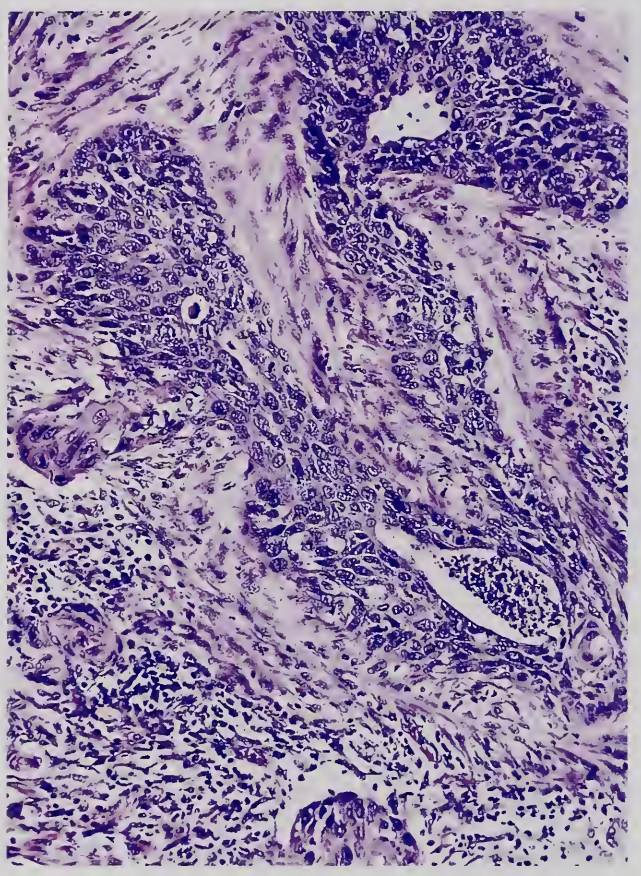


Figure 6-5

INVASIVE SQUAMOUS CELL CARCINOMA

Irregularly shaped nests of atypical epithelium with basaloid and squamous differentiation are surrounded by desmoplastic, inflamed stroma.

Table 6-1

TNM AND FIGO CLASSIFICATION OF CARCINOMAS OF THE VAGINA[a,b]

TNM Categories	FIGO Stages	
T - Primary Tumor		
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	0	Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumor confined to vagina
T2	II	Tumor invades paravaginal tissues but does not extend to pelvic wall
T3	III	Tumor extends to pelvic wall
T4	IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond the true pelvis
Note: the presence of bullous edema is not sufficient evidence to classify a tumor as T4.		
M1	IVB	Distant metastasis

N - Regional Lymph Nodes[c]	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M - Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IVA	T4	N0	M0
Stage IVB	Any T	Any N	M1

[a]Modified from Tavassoli FA, Deville P. Pathology and genetics of tumours of the breast and female genital organs. International Agency for Research on Cancer. World Health Organization. Lyon: IARC Press; 2003:292. A help desk for specific questions about TNM classification is available at http://www.uicc.org.

[b]FIGO = International Federation of Gynecologists and Obstetricians.

[c]The regional lymph nodes are: upper two-thirds of vagina: the pelvic nodes including obturator, internal iliac (hypogastric), external iliac, and pelvic nodes, NSO; lower third of vagina: the inguinal and femoral nodes.

nodes and distant sites including the lung, liver, and brain. Recurrence is typically local and usually develops within 2 years of treatment.

Surgical treatment is similar to that of cervical and vulvar cancer and is based on the location of the vaginal neoplasm relative to the cervix or vulva. Radiation therapy, however, is the primary form of treatment for vaginal carcinoma. Tumors in the upper portion of the vagina, like cervical carcinomas, gain access to lymphatics that drain to the pelvic side wall whereas tumors involving the lower portion of the vagina, like vulvar carcinomas, invade lymphatics that drain to the inguinal-femoral nodes. The prognosis had been poor in the past because of late detection and because the rich vascular and lymphatic supply of the vagina permits early invasion. Survival has improved in recent years, however, with reported 5-year survival rates of 77 percent for stage I/II tumors and 56 percent for stage III/IV tumors (62,72,94). In multivariate analyses, only size and stage are significant prognostic factors. Failure to control local growth is the usual cause of death.

An increased risk of second cancers following vaginal cancer has been reported (131). Most of

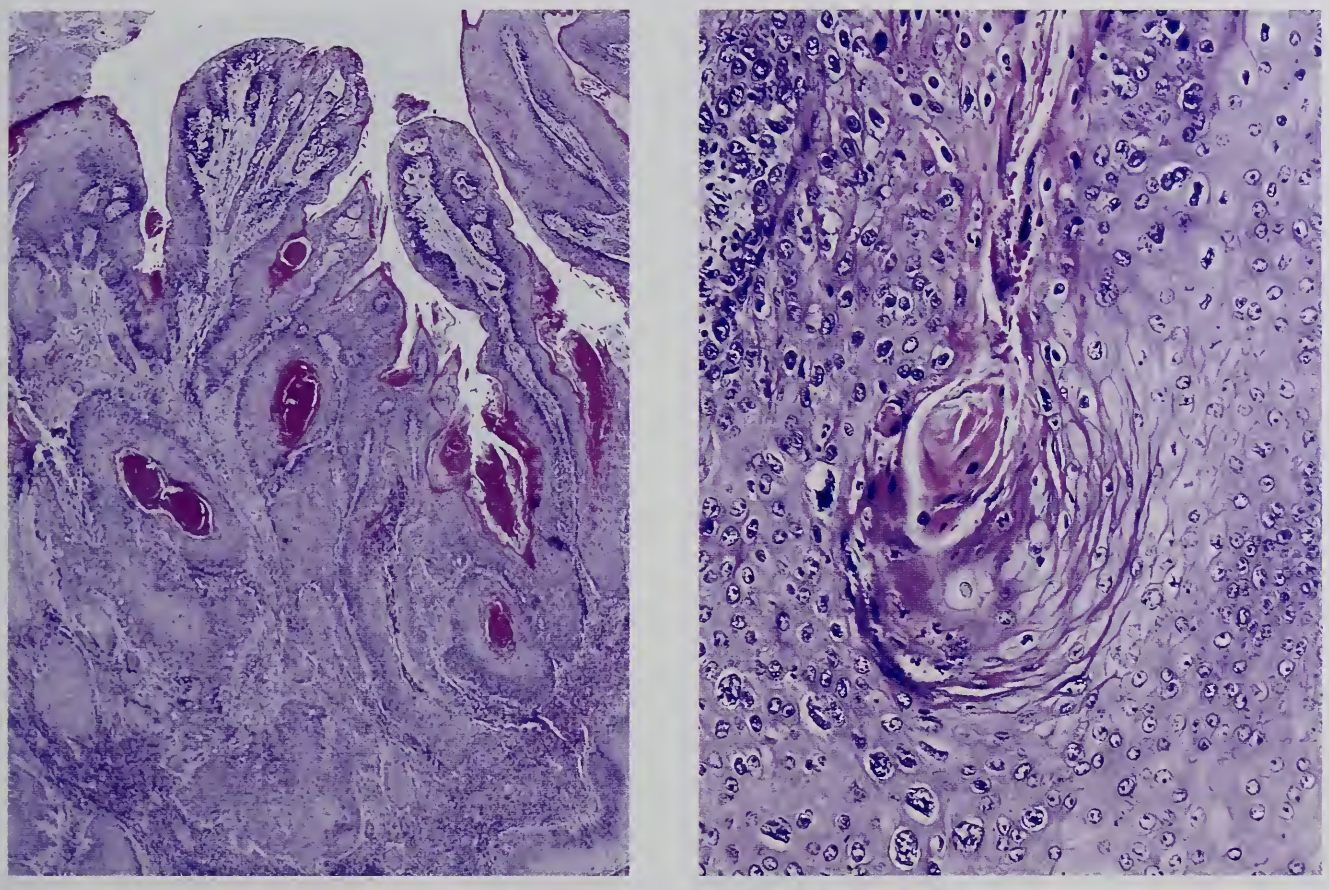


Figure 6-6

WARTY (CONDYLOMATOUS) CARCINOMA

Left: This variant of squamous cell carcinoma exhibits verruciform architecture.
Right: Atypical squamous epithelium exhibits prominent "viral cytopathic effect" (koilocytosis).

these cancers are smoking related (lung, buccal cavity, pharynx, esophagus, nasal cavity, and larynx) or related to infection of the anogenital tract with HPV (cervix, vulva, and anus).

Verrucous Carcinoma

Verrucous carcinoma of the vagina has the same appearance as in the cervix and vulva and is described in greater detail in those chapters. In the lower female genital tract, verrucous carcinoma occurs most often in the vulva, followed by the cervix and then vagina. Because of the wide variety of terms used and differing diagnostic criteria, it is difficult to ascertain the precise number of cases reported (21). The tumor characteristically recurs locally and can be successfully treated by wide local excision. Because of their large size, some tumors must be treated by exenteration, abdominoperineal resection, and vaginectomy. The 5-year survival rate is 70 percent. Invasive squamous cell carcinoma occasionally accompanies or follows verrucous carcinoma.

Warty (Condylomatous) Carcinoma

Squamous cell carcinomas with striking condylomatous features microscopically are designated *warty carcinomas* (106). Similar to verrucous carcinomas, warty carcinomas appear to be less aggressive than typical well-differentiated squamous cell carcinomas, although the experience with warty carcinoma is limited. Microscopically, warty carcinoma has the features of a squamous cell carcinoma at the deep margin, but has striking condylomatous features.

Unlike verrucous carcinoma, the exophytic papillary growths in warty carcinoma contain fibrovascular cores. Many of the malignant cells display "viral change" resembling the koilocytotic atypia in SILs and greater nuclear atypia than verrucous carcinoma (fig. 6-6).

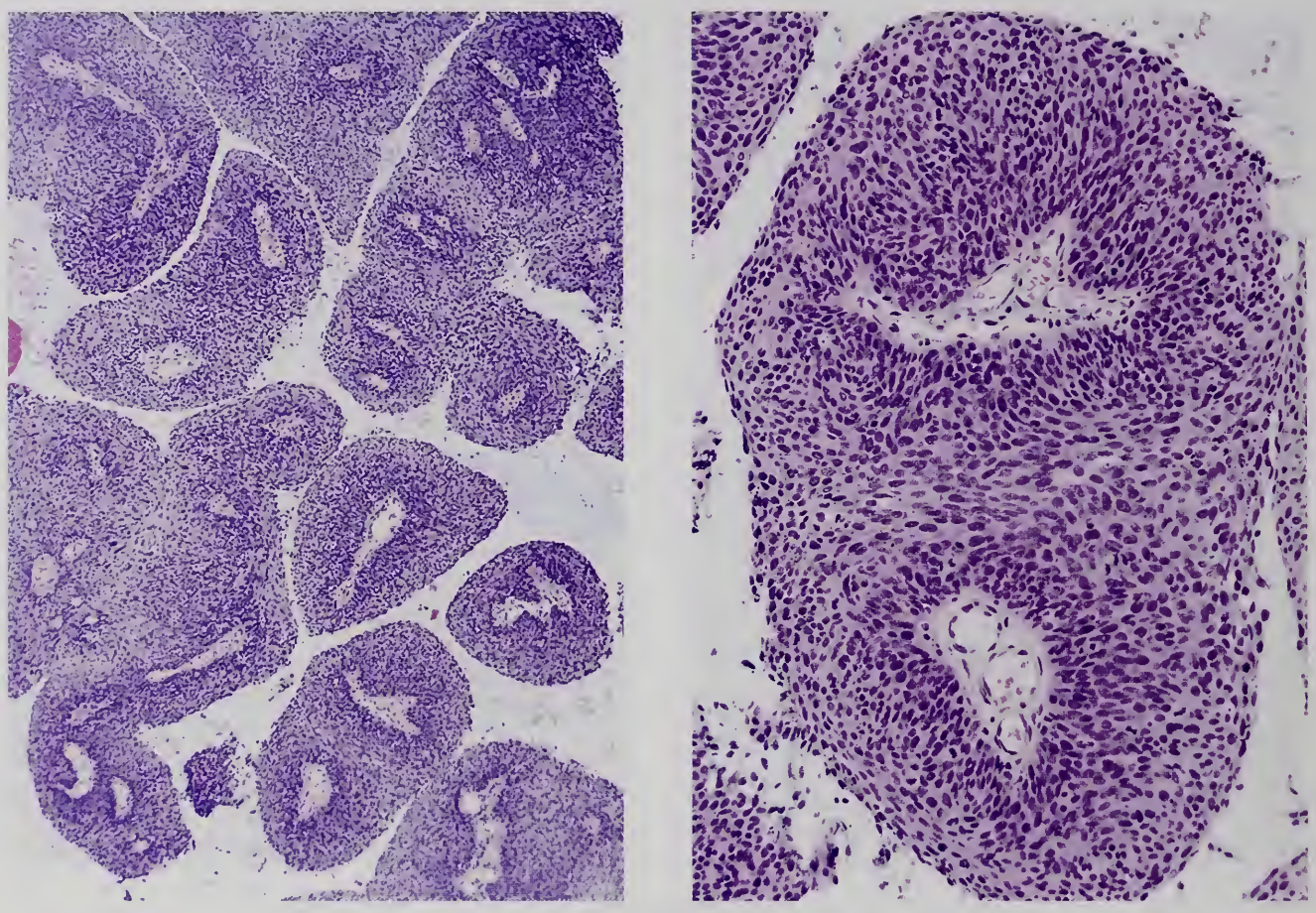


Figure 6-7

PAPILLARY SQUAMOUS (SQUAMOTRANSITIONAL) CELL CARCINOMA

Left: This variant of squamous cell carcinoma has a basaloid/transitional appearance and forms papillary structures containing fibrovascular cores.

Right: This tumor is lined by epithelium identical to that seen in high-grade squamous intraepithelial lesion (HSIL) which covers papillary structures containing fibrovascular cores. Evaluation of the underlying stroma is required to distinguish in situ from invasive lesions.

Papillary Squamous (Squamotransitional) Cell Carcinoma

A few *papillary squamous (squamotransitional) cell carcinomas* identical to those that occur in the cervix have been reported (fig. 6-7) (116). These tumors are also termed *papillary squamotransitional cell carcinoma*. The presence of HPV 16 supports a close relationship to the usual type of squamous cell carcinoma.

GLANDULAR LESIONS

Adenosis

Definition. *Adenosis* is the presence of glandular epithelium in the vagina.

General Features. The vagina is lined entirely by squamous epithelium and is normally devoid of glands. The presence of glands in the vagina was first described by von Preuschen (141), and was designated "adenomatosis vaginae" by Bonney and Glendining (9). Subsequently, Plautt and Dreyfuss (100) coined the term "adenosis."

In 1971, adenosis was determined to be related to prenatal DES exposure (56), occurring in approximately one third of the exposed offspring (52). In these women, the frequency of detection of adenosis depended on several factors: the manner in which the patient presented for examination, the dosage of DES during pregnancy, the time in pregnancy when the DES was first given, and the age of the patient

at the time of examination (88). Before 1971, adenosis was rarely reported.

In an autopsy study of 100 fetuses, children, and young women not exposed to DES in whom the vaginas were extensively sampled, adenosis was detected in only 8 cases (66). Because adenosis is usually asymptomatic, it occurs more commonly than is generally recognized in the absence of careful vaginal examination.

The embryologic basis for the development of adenosis in the DES-exposed woman is described in chapter 1. During gestation, DES inhibits the urogenital-derived squamous epithelium destined to become the vaginal epithelium from normally growing up to the junction of the ectocervix and endocervix and replacing the preexisting müllerian-derived columnar epithelium. The embryonic müllerian epithelium that is not replaced persists and develops into adenosis. Similar findings have been reported in animals, including mice and rhesus monkeys treated with DES during pregnancy (31,60,99). In unexposed women, adenosis probably also arises on a congenital basis, remaining latent throughout childhood, and becoming evident after puberty, perhaps as a result of the influence of steroid hormones (59,66). The adenosis seen in DES-unexposed and -exposed women is microscopically identical (111).

Gross structural abnormalities of the cervix occur in about 25 percent of DES-exposed women and are rare in women who are unexposed. The structural abnormalities include cervical hypoplasia, cervical hoods, transverse vaginal septa, pseudopolyps, and obliteration of the vaginal fornices (51).

Adenosis characterized by the presence of glands lined by mucinous or endometrial type epithelium has been described in the vagina after laser vaporization or intravaginal application of topical 5-fluorouracil for the treatment of extensive vaginal condylomas. The development of adenosis in these patients is probably related to the extensive denuding of the epithelium, but the precise etiology of the lesion in this setting is unknown (120).

Clinical Features. Most women with adenosis are asymptomatic; some, however, present with mucous discharge or bleeding. Areas of adenosis and associated squamous metaplasia are usually visible by colposcopy and iodine staining. Adenosis is found in the upper third of the vagina in 75 percent of cases, although it may be found at any level. The anterior wall is most commonly involved.

Gross Findings. Adenosis is present as multiple cysts from 0.5 to 4.0 cm in diameter or as mucosa that is diffusely red and granular. Colposcopic examination reveals columnar and metaplastic squamous epithelium.

Microscopic Findings. Adenosis is characterized by the presence of glands in the lamina propria by the replacement or covering of the surface squamous epithelium by glandular epithelium. The glands are lined by three types of epithelium, sometimes mixed: the most common, mucinous epithelium resembling endocervical epithelium; simple or pseudostratified cuboidal or columnar cells, at least some of which are ciliated, resembling the epithelium of the fallopian tube or endometrium (tuboendometrial type); and the rare epithelium composed of cuboidal embryonic type cells with scant cytoplasm lining tiny glands that lie at the junction of the squamous epithelium and the lamina propria (fig. 6-8).

The distribution of adenosis correlates with its cellular composition. Adenosis on the surface is almost always of the mucinous type whereas glands in the lamina propria are mucinous or tuboendometrial type. In the upper vagina, mucinous epithelium is more common than tuboendometrial epithelium. In the distal vagina, adenosis is less frequently encountered, and the tuboendometrial type is more common than the mucinous type.

Squamous metaplasia, replacing the glandular epithelium of adenosis to some extent, is typically present. At first the metaplasia is immature, but later it matures, becomes glycogenated, and eventually replaces the gland lumens. In the final stages of the replacement of glands by squamous metaplasia, the only vestige of adenosis may be the presence of intercellular pools of mucin or mucin droplets within the squamous epithelial cells. A lymphocytic and plasma cell infiltrate frequently surrounds glands of adenosis or is present beneath the columnar epithelium on the surface. Neutrophils are less commonly observed.

Microglandular hyperplasia identical to that occurring in the cervix may develop in women

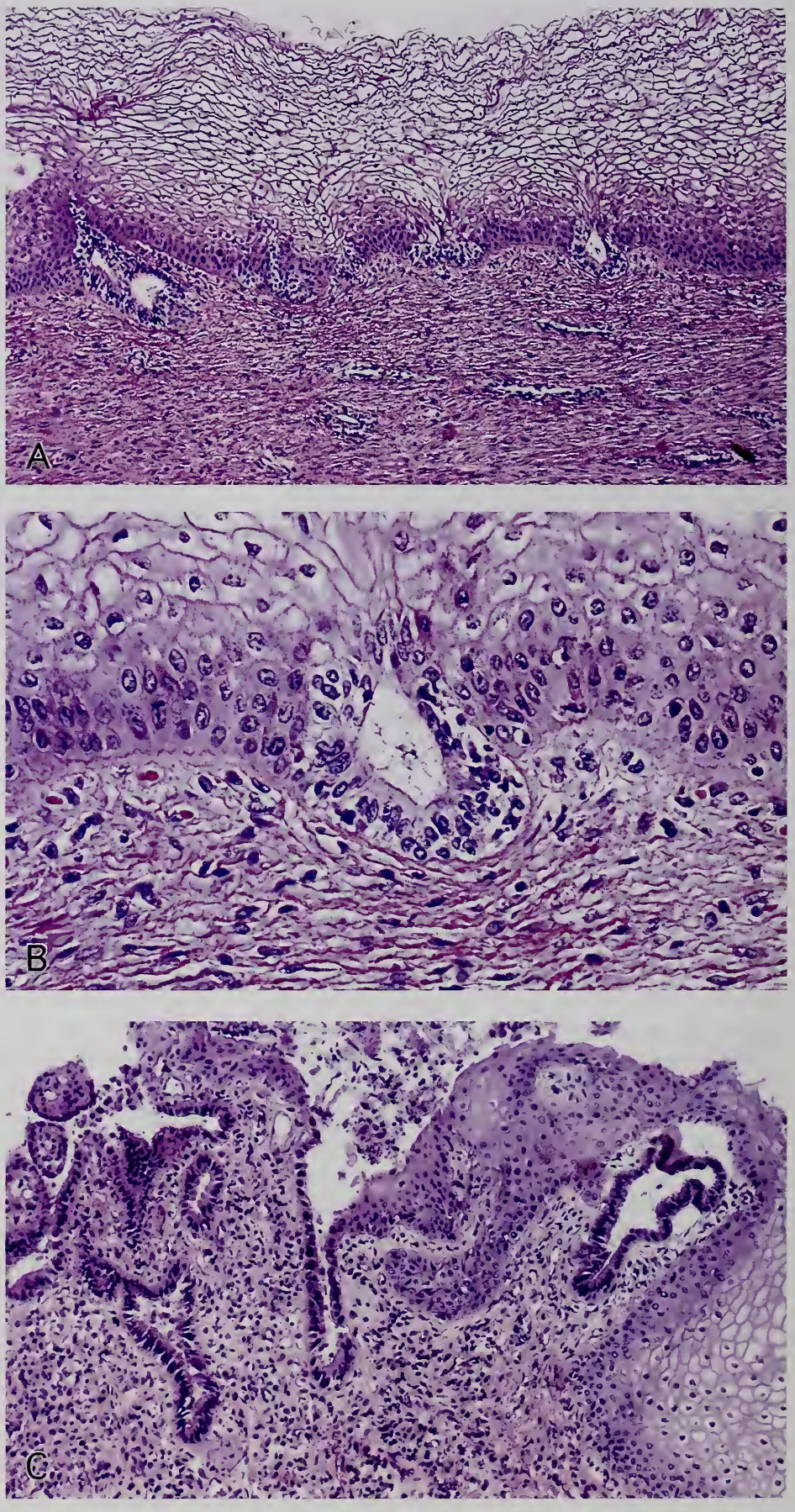


Figure 6-8

VAGINAL ADENOSIS

A: Vaginal mucosa from a fetus (28 weeks) contains two foci of glandular epithelium intimately associated with the basal layer.

B: At higher magnification, the glandular epithelium arises from the basal layer of the squamous mucosa.

C: The genesis of adenosis from the basal layer is demonstrated.

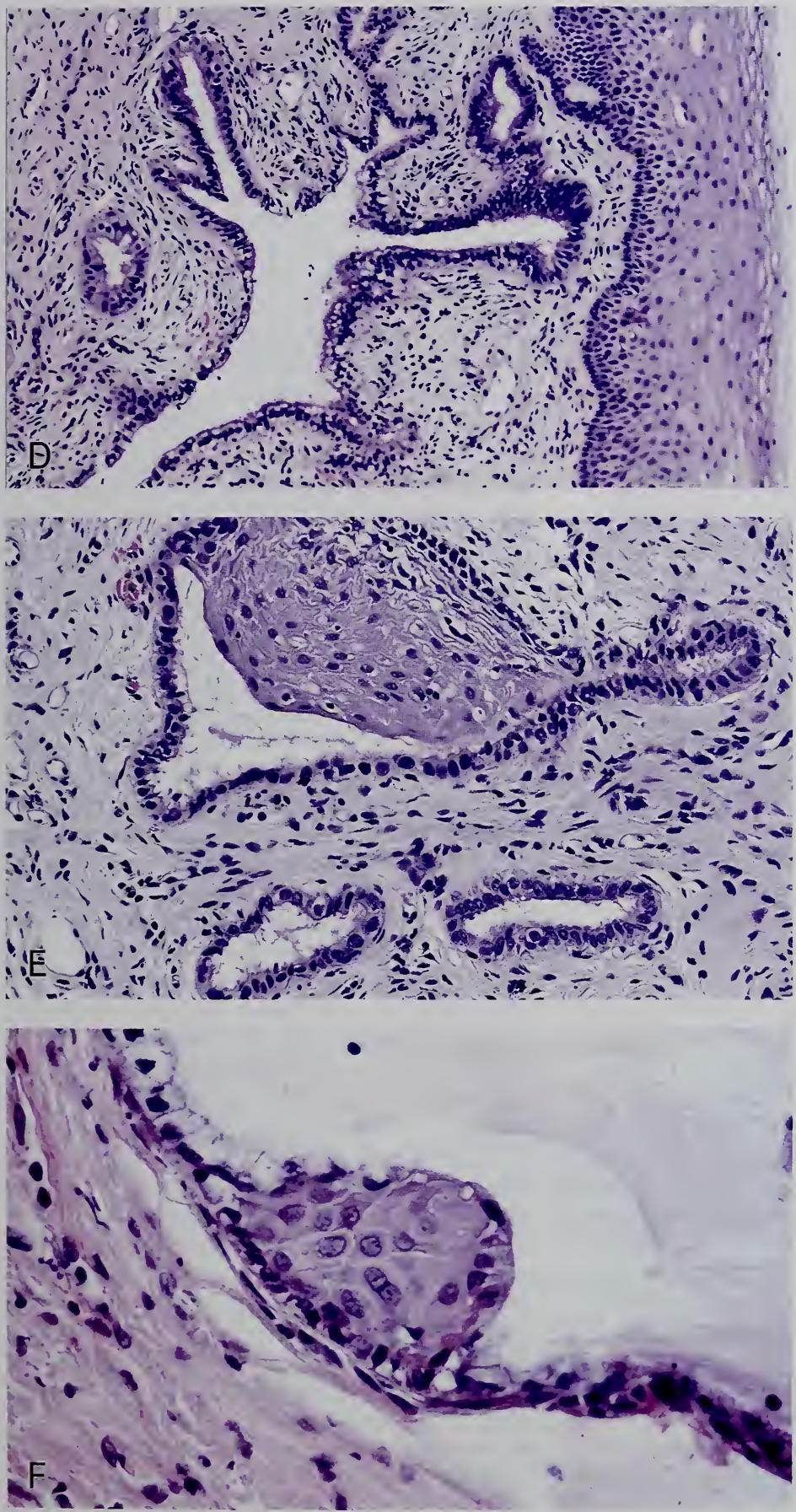


Figure 6-8 (Continued)

D: Tuboendometrioid type of adenosis is present in the superficial stroma of the vaginal mucosa.

E: Tuboendometrioid type of adenosis is partially replaced by squamous metaplastic epithelium.

F: Early squamous metaplasia focally replaces the glandular epithelium in this example of mucinous (endocervical type) adenosis.

with adenosis who are on oral contraceptives (see chapter 5).

Cytologic Findings. Detection of columnar or metaplastic squamous cells from the middle and upper third of the vagina is helpful in the diagnostic evaluation of women suspected of having been exposed to DES in utero. However, similar findings occur in 10 percent of unexposed women, probably as result of contamination of the vaginal specimen by columnar or metaplastic squamous cells from the cervix (113).

Differential Diagnosis. Mesonephric (Gartner duct) remnants, particularly when hyperplastic, may be confused with adenosis. Unlike adenosis, which tends to be superficial in the anterior wall, mesonephric remnants are mostly deep in the lateral walls. At their terminations, however, they may be superficial. Mesonephric structures are composed of closely grouped tubules, often clustered around a duct, and are lined by a single layer of cuboidal cells containing uniform, round nuclei with granular chromatin. Dense, eosinophilic, periodic acid–Schiff (PAS)-positive nonmucinous material is characteristically found in the lumens, and loose vascular stroma, distinctly different from the fibromuscular stroma of the vagina, often surrounds the tubules.

Endometriosis may be confused with adenosis. Unlike adenosis, the glands of endometriosis are surrounded by endometrial stroma and may be associated with old or recent hemorrhage.

Extensive vaginal adenosis that is replaced by immature metaplastic squamous epithelium may simulate invasive squamous cell carcinoma. The absence of significant cytologic atypia and the uniform rounded outlines of the nests, in contrast to the more irregular contours of the nests of squamous cell carcinoma, facilitate the diagnosis.

Treatment and Prognosis. Follow-up studies indicate that adenosis spontaneously regresses in the majority of patients (4,83). Because of the risk of the development of clear cell carcinoma, patients should be carefully followed, but treatment of the adenosis is unnecessary.

Atypical Adenosis

Atypical adenosis occurs in tuboendometrial epithelium. The atypical glands tend to be more complex than the glands of typical adenosis and are lined by enlarged cells with atypical nuclei. The latter are pleomorphic and hyperchromatic, and contain prominent nucleoli. Mitotic figures are infrequent and hobnail cells may be present (fig. 6-9). Whereas benign-appearing tuboendometrial adenosis is euploid or polyploid, the cells in atypical adenosis are aneuploid (36).

The frequent finding of atypical adenosis lined by tuboendometrial, in contrast to mucinous, epithelium immediately adjacent to clear cell adenocarcinoma suggests that atypical adenosis may be the precursor of clear cell carcinoma (114,115). Although clear cell carcinoma has been shown to develop in patients with adenosis (118), no case of atypical adenosis has been reported to progress to clear cell carcinoma, and therefore, definitive proof that atypical adenosis is premalignant is lacking.

Endometriosis

The combination of endometrial glands and stroma is diagnostic of *endometriosis*. Sometimes the presence of hemorrhage; macrophages filled with hemofuscin, hemosiderin, or both; and granulation tissue obscures the picture. In particular, because endometrial type stroma may be scant in endometriotic lesions in this location, confusion with adenocarcinoma or adenosis may occur. The absence of significant cytologic atypia and mitotic activity permits distinction from adenocarcinoma. In patients who are pregnant or on high-dose progestational drugs, decidualization may lead to confusion with a nonkeratinizing squamous cell carcinoma. Immunostains for high molecular weight cytokeratins distinguish squamous cell carcinoma, which is diffusely positive, from decidua, which is negative.

Endocervicosis

A case of *endocervicosis* of the vagina presenting as a tumor-like mass associated with right lower quadrant pain has been reported (74). The lesion was thought to have arisen from implantation of cervical tissue at the time of a hysterectomy, since the patient's symptoms began shortly after the procedure and symptoms disappeared after excision of the lesion. Microscopically, endocervicosis is composed of glands lined by endocervical type epithelium; the glands display an infiltrative type growth pattern.

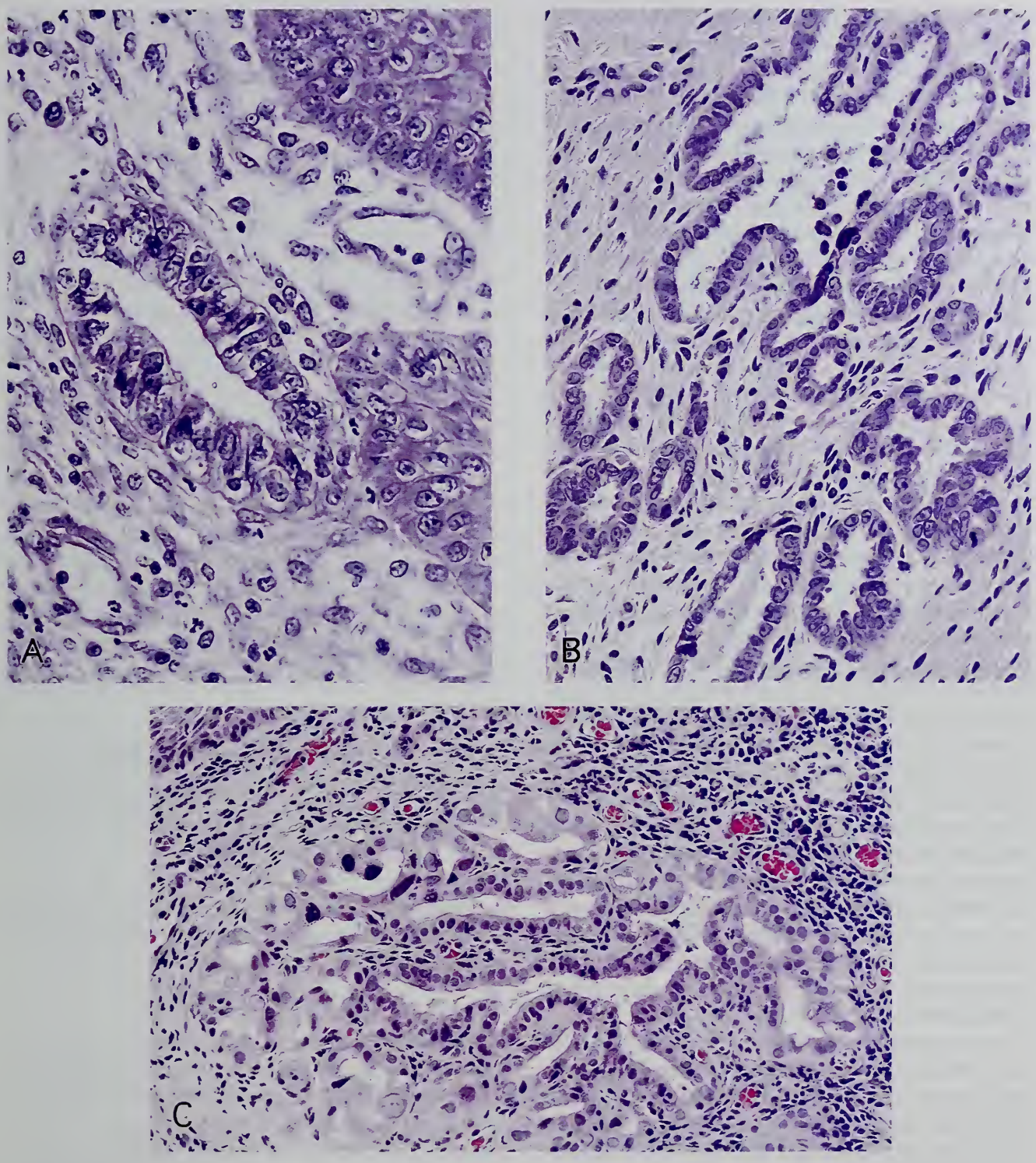


Figure 6-9

VAGINAL ATYPICAL ADENOSIS

A: Tuboendometrioid type of adenosis exhibits some nuclear atypia.

B: Tuboendometrioid type glands within adenosis adjacent to a vaginal adenocarcinoma in a woman with a history of diethylstibestrol (DES) exposure exhibit cytologic atypia characterized by enlarged nuclei with evident nucleoli. Some cells have hyperchromatic nuclei and a few have hobnail features.

C: Vaginal adenosis with superimposed Arias-Stella reaction. The glands within the stroma of vaginal mucosa contain some hobnail cells characterized by hyperchromatic nuclei identical to those encountered in gestational endometrium. In this location, the lesion can be misclassified as atypical adenosis or clear cell carcinoma.

The differential diagnosis includes well-differentiated mucinous adenocarcinoma and vaginal adenosis. Primary vaginal mucinous carcinomas are rare. The absence of cellular atypia and mitotic activity in endocervicosis distinguishes it from adenocarcinoma. A mucinous adenocarcinoma arising in vaginal endocervicosis has been reported (76). The patient presented with bilateral groin lymph node metastases and the tumor recurred within a year after treatment. Unlike endocervicosis, adenosis is superficial, lacks an infiltrative pattern, and does not form a tumor-like mass.

Cysts

Vaginal cysts are not common and usually do not present a problem in the differentiation from tumors. Cysts are classified according to their epithelial lining (25). Most are *squamous epithelial inclusion cysts* resulting from surgical trauma and the implantation of squamous epithelium beneath the surface. This type of cyst is usually single and located in the posterior or lateral wall of the vagina at the site of a previous episiotomy.

Müllerian-derived cysts are lined by columnar, mucin-secreting, endocervical type epithelium. Ciliated tubal type epithelium and squamous metaplasia may also be encountered. These cysts should be distinguished from adenosis, which may also be focally cystic. In contrast to adenosis, a müllerian cyst is a single large structure that is typically visible on gross examination and may be associated with pain and dyspareunia. Vaginal adenosis does not present clinically as a single large cyst but rather as multiple smaller cysts and on microscopic examination is composed of numerous small glands in the lamina propria.

Mesonephric cysts, also termed *Gartner duct cysts*, are rare. They tend to be smaller than müllerian cysts, usually not exceeding 2 cm, and are located in the lateral vaginal wall. They are lined by nonmucin-secreting cuboidal or low columnar epithelial cells. Cilia are absent and foci of squamous metaplasia are unusual. *Mesonephric remnants*, in the form of a mesonephric duct and tubules, are infrequently encountered (fig. 6-10). These structures may be confused with adenosis.

Urothelial cysts are usually less than 1 cm, and are typically found in the distal vagina in a suburethral location. They are lined by transitional epithelium, but stratified cuboidal or columnar epithelium may be admixed; cilia are not present.

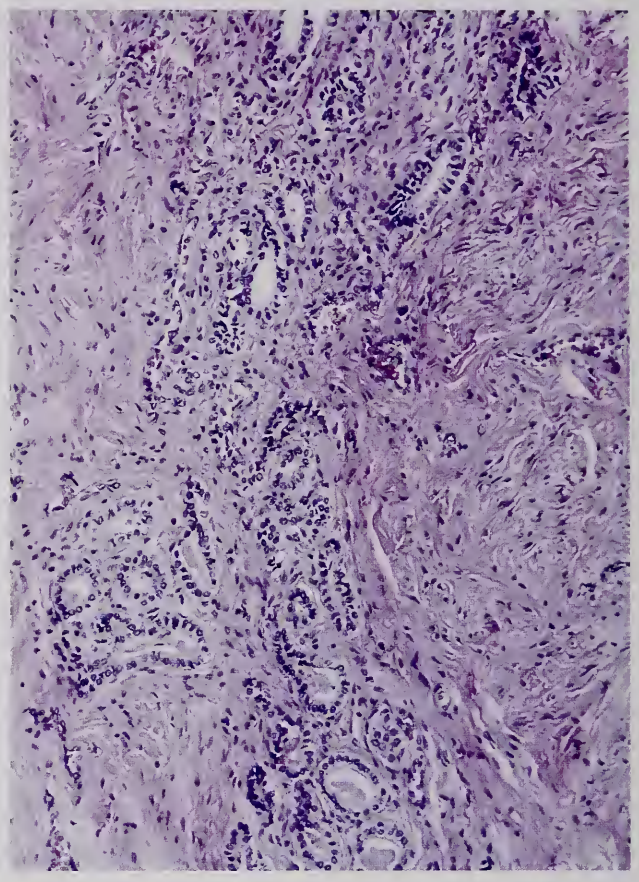


Figure 6-10

MESONEPHRIC REMNANTS IN VAGINA

Small tubular glands lined by cuboidal epithelium and containing eosinophilic secretions are identical to the mesonephric remnants found in the cervix but in this location they simulate adenosis.

Müllerian Papilloma

Müllerian papilloma arises in the vagina and cervix of infants and young girls; it has been reported in a 24-year-old woman who was pregnant at the time of the diagnosis (75). Müllerian papilloma is a benign papillary tumor composed of connective tissue fronds covered by cuboidal or mucinous epithelium. Occasionally, some of the cells have a hobnail appearance, suggesting a clear cell carcinoma; however, there are no clear cells and cytologic atypia and mitotic activity are absent. The origin of the tumor is not clear, although reports suggest a müllerian origin (136).

ENDOMETRIOID, ENDOCERVICAL, AND INTESTINAL TYPE ADENOCARCINOMAS

Before 1971, when the association between in utero DES exposure and clear cell adenocarcinoma was first made (55), adenocarcinoma of the vagina accounted for only 5 to 10 percent of vaginal carcinomas (33). With the increased number of clear cell adenocarcinomas recognized after 1971, the frequency rose to nearly 25 percent of all vaginal carcinomas in 1988. It is likely that this figure will decline, in view of the discontinuation of DES usage in pregnancy.

Before the müllerian derivation of clear cell carcinoma was established (55), adenocarcinomas were classified as either adenocarcinoma not otherwise specified or mesonephroma. It is now recognized that the former group is composed of endometrial type (endometrioid) and mucinous carcinomas and the latter of clear cell carcinomas, rare yolk sac tumors, and a few examples of true mesonephric carcinomas. There have been only a few cases of endometrioid carcinoma reported. Almost all have been recorded in the older American and foreign literature specifically to cite their relationship to vaginal adenosis.

Endometrioid carcinoma of the vagina has the same histologic appearance as its more common counterpart in the endometrium. A few cases of endometrioid carcinoma associated with adenosis have occurred in DES-exposed offspring; others have risen in vaginal endometriosis (45,77). *Mucinous carcinoma* may resemble typical endocervical (17) or intestinal (32) adenocarcinoma. The histologic appearance of this tumor in the vagina is similar to that of its counterpart in the cervix. Because of the rarity of endometrioid, endocervical, and intestinal carcinomas, little is known of their etiology and behavior.

Clear Cell Adenocarcinoma

Definition. *Clear cell adenocarcinoma* is an adenocarcinoma displaying a solid, tubulocystic, or papillary pattern in which most of the cells are clear cells or hobnail cells.

General Features. From the 1970s to the 1990s, most cases of vaginal clear cell carcinoma occurred in young women with a history of DES exposure in utero. By 1999, slightly more than 700 patients with clear cell adenocarcinoma had been accessioned to the Registry for Research on Hormonal Transplacental Carcinogenesis, with an estimated 25 to 50 new cases developing each year (48). Approximately 60 percent of these patients had documented exposure in utero to DES, dienestrol, or hexestrol, and another 12 percent were exposed to an unknown medication usually for a high-risk pregnancy. Approximately 2 million women were exposed in utero to these drugs in the United States and a smaller number were exposed in Canada, Western Europe, Australia, Mexico, and Africa. Since the removal of DES from the market for the treatment of high-risk pregnancy in 1971, the exposed population has aged and fewer DES-associated cases are currently identified in the United States.

The age distribution for clear cell carcinoma involving the vagina and cervix is bimodal for DES exposed women. The first peak occurs at a mean age of 26 years and the second peak at a mean age of 71 years (44). Two thirds of the younger women have tumors involving the vagina, whereas two thirds of the older women have tumors involving the cervix.

In the exposed woman up to the age of 24 years the risk of development of this form of cancer is 0.014 to 0.14 percent (49). Thus, although DES is a carcinogen in humans and many other species, the rarity of clear cell carcinoma in the exposed population suggests that it is an incomplete carcinogen and that other factors are necessary to produce neoplastic transformation. Factors that appear to increase the risk of clear cell carcinoma are exposure to DES before the 12th week of pregnancy, maternal history of a prior spontaneous abortion, and conception in the fall (144). Since most of the carcinomas are first detected between the time of puberty and the decade thereafter, endogenous steroid hormones have been suspected to play a role. There is substantial experimental evidence that DES is a teratogen that leads to congenital anomalies of the upper and lower female genital tract, such as vaginal adenosis, cervical ectropion, and a variety of gross structural abnormalities of the cervix. In over 90 percent of patients with clear cell carcinoma, adenosis is found immediately adjacent to the tumor and is thought to be its likely precursor (52).

Molecular studies have demonstrated a high frequency of microsatellite instability in vaginal clear cell carcinoma (10). Overexpression of wild type p53 is also very common, frequently accompanied by strong expression of bcl-2. Apoptosis is not usually present, suggesting that bcl-2 inhibits p53 apoptosis (143).

HPV 31 has been detected by polymerase chain reaction (PCR) in 3 of 14 vaginal clear cell carcinomas (142). HPV may be a cofactor in the development of these tumors but not as important as in squamous and nonclear cell carcinomas because the association is less frequent.

Clinical Features. Women with clear cell carcinoma range in age from 6 to 42 years, with a peak between 19 and 26 years; most are less than 30 years of age. Vaginal bleeding and discharge are the most common complaints, but a significant number of women are asymptomatic. An abnormal vaginal cytologic specimen may lead to detection, but is negative in a substantial number of cases (133).

Approximately 60 percent of clear cell carcinomas are confined to the vagina, usually in the upper third of the anterior wall, however, any part of the vagina may be involved. Vaginal clear cell carcinoma also involves the cervix.

Gross Findings. Most clear cell carcinomas are polypoid, nodular, or papillary, but some are flat or ulcerated. Small tumors, particularly those confined to the lamina propria, may be invisible on gross or even colposcopic examination and are only detected by palpation. Large tumors are up to 10 cm in greatest dimension.

Microscopic Findings. Clear cell carcinoma of the vagina has an appearance similar to clear cell carcinoma of the cervix, endometrium, and ovary. Although the tumor is named for the clear cell, the predominant cell type is usually the hobnail cell, characterized by inconspicuous cytoplasm and a bulbous nucleus that protrudes into glandular lumens (figs. 6-11, 6-12). The clear cell is characterized by abundant intracytoplasmic glycogen, which accounts for the clear cytoplasm (fig. 6-12). The tumor cells may be flat with bland nuclei and scant cytoplasm. Nonglycogenated cells that are not flat or hobnail have granular eosinophilic cytoplasm and are usually intermingled with the other cell types. The nuclei vary considerably in appearance. Significant enlargement and atypia may be present in clear and hobnail cells, but flat cells are typically bland. Mitotic activity is also variable but is usually low.

Clear cell carcinomas display a variety of patterns described as solid, tubulocystic, and papillary (fig. 6-12). The tubulocystic pattern is the most common. Solid areas tend to be composed of sheets of clear or eosinophilic cells. The tubulocystic areas are usually lined by flattened, clear, or hobnail cells. Tumors displaying a tubulocystic pattern, in which the predominant cell is the flattened cell, appear bland and may be erroneously interpreted as benign or atypical adenosis. Adenosis is not composed of flattened cells; instead, the glands are lined by cuboidal or columnar epithelium. Papillary areas of clear cell carcinoma are usually lined by clear or hobnail cells. Psammoma bodies and intracellular hyaline bodies may be encountered. Although mucin is present within gland lumens, it is rarely found intracytoplasmically.

DNA Ploidy Patterns. Four patterns of nuclear DNA distribution have been described: 1) peridiploid stem cell lines (2N to 3N); 2) peritetraploid stem cell lines (3N to 5N); 3) hypertetraploid stem cell lines (5N); and 4) highly aneuploid without detectable stem cell lines (146). The first two patterns are associated with stages I and II tumors, whereas the last two patterns are more often associated with stages III and IV disease. Although these findings suggest that ploidy may have prognostic significance, they are inconclusive because only a few high-ploidy low-stage tumors have been examined. Patients with clinically advanced tumors have a poor prognosis, regardless of ploidy level.

Cytologic Findings. In cellular preparations, the malignant cells occur singly or in clumps and resemble large endocervical cells. The nuclei are large with a prominent nucleolus. Occasionally, nuclear atypia is only minimal; bizarre nuclei may be present. The cytoplasm is delicate (133). Although clear cell carcinomas can be detected cytologically, the results have been reported as "positive" or "suspicious" in only 74 percent of specimens. Part of the problem may be the method of collection. A routine smear from the cervix may not detect a vaginal neoplasm. In addition, the bland cytologic features of some tumors and the presence of a marked inflammatory infiltrate, contribute to the difficulty of cytologic detection.

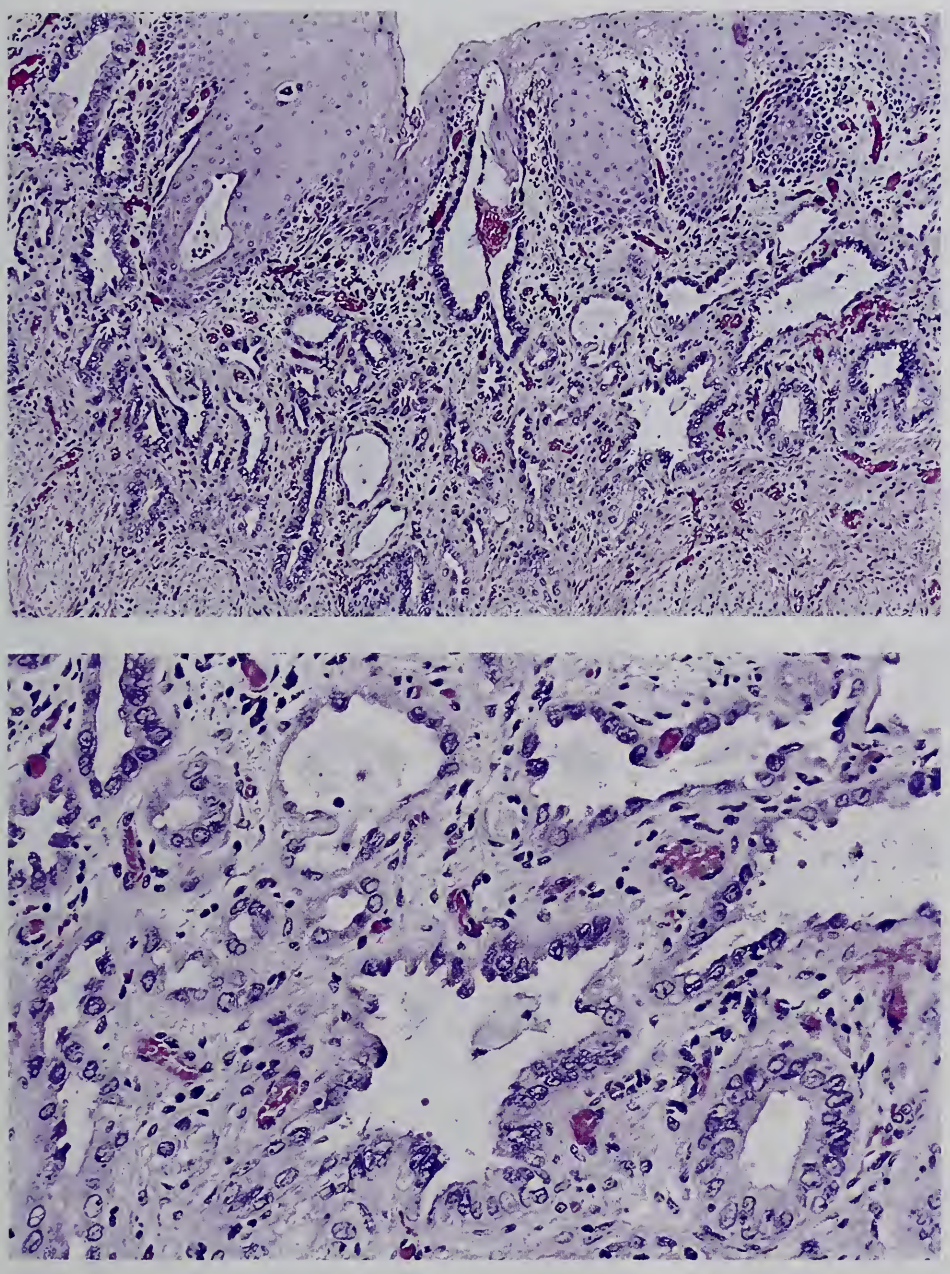


Figure 6-11

EARLY CLEAR CELL CARCINOMA ARISING IN ASSOCIATION WITH ATYPICAL ADENOSIS

Top: Variably sized atypical glands fill the superficial stroma of the vaginal mucosa.

Bottom: Higher magnification demonstrates glands lined by atypical cells, some with hobnail morphology and some with enlarged vesicular nuclei with prominent nucleoli.

Differential Diagnosis. The lesions most commonly considered in the differential diagnosis are microglandular hyperplasia and the Arias-Stella reaction arising in adenosis. The glands of microglandular hyperplasia are smaller and usually more densely packed than those in clear cell carcinoma. In addition, in microglandular hyperplasia, mitotic activity is inconspicuous, cytologic atypia is minimal or absent, and squamous metaplasia is often present.

The Arias-Stella reaction almost never displays mitotic activity and lacks the papillary architecture often seen in clear cell carcinoma. Nuclear atypia may be marked in the Arias-Stella reaction, with hobnail type cells simulating the hyperchromatic hobnail cells of clear cell carcinoma; however, the nuclear chromatin in these cells is smudged and degenerative in appearance whereas in clear cell carcinoma many tumor cells have nuclei with vesicular chromatin and prominent nucleoli or chromatin that is granular but not degenerative in appearance. Immunostains for Ki-67 confirm a low proliferation index in these benign lesions whereas increased activity is seen in clear cell carcinoma.

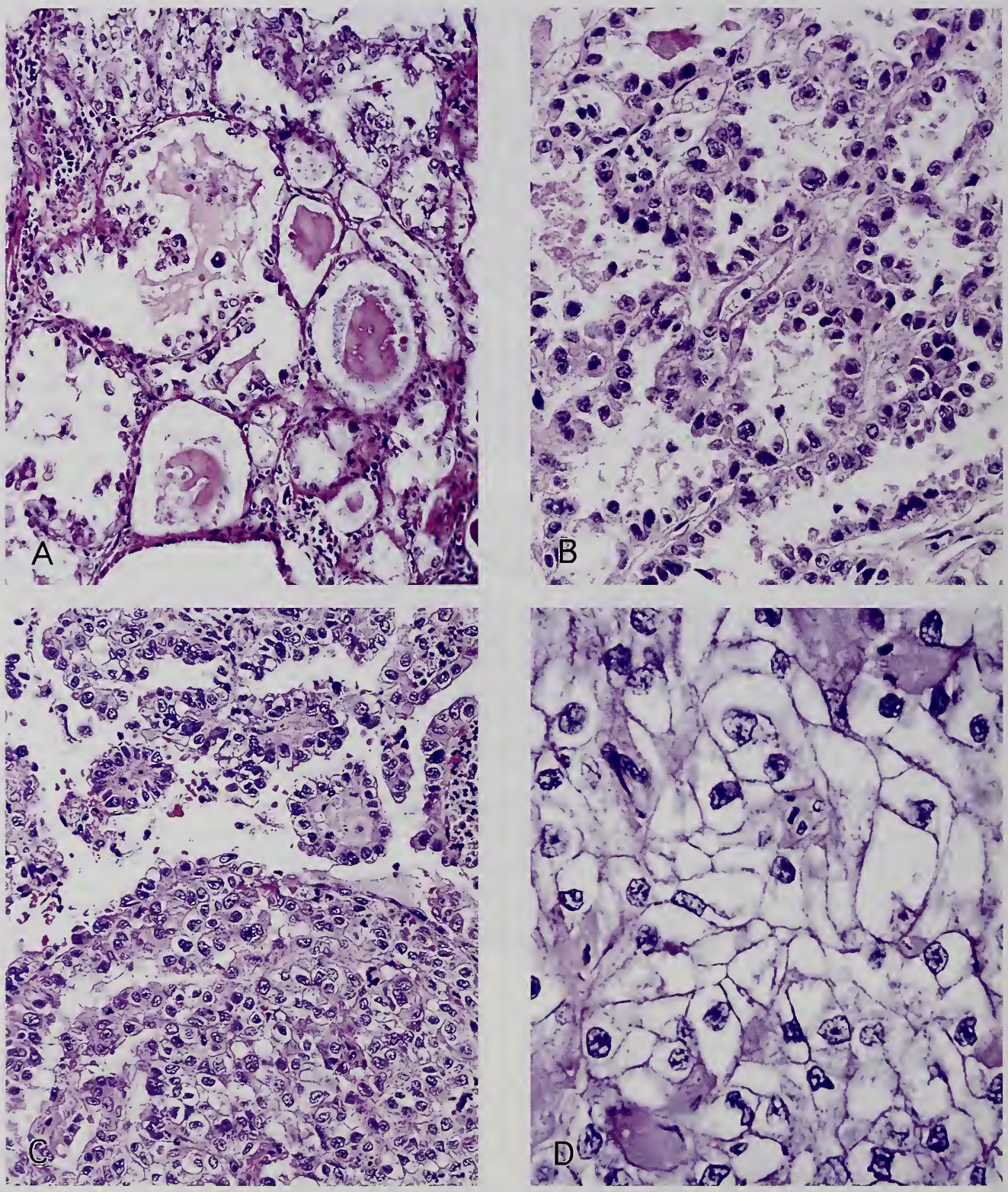


Figure 6-12

CLEAR CELL CARCINOMA

A: The tubulocystic (glandular) pattern is characterized by tubular and cystic glands lined by clear and hobnail cells.
B: Tubular glands are lined by atypical hobnail cells with eosinophilic (oxyphilic) cells rather than clear cytoplasm.
C: Papillary and solid architectural patterns are evident; all cells have abundant clear cytoplasm.
D: Solid pattern of tumor contains cells with abundant clear cytoplasm.

Treatment and Prognosis. Clear cell carcinoma spreads by local invasion and lymphatic and hematogenous metastases. Recurrence appears in 25 percent of the patients. Spread to pelvic lymph nodes occurs in 16 percent of patients with stage I disease (53). The risk of lymph node metastasis increases dramatically with invasion beyond 3 mm; nonetheless, lymph node metastasis occurs in 5 percent of patients with stage I disease with invasion less than 3 mm (54). Pelvic lymph node metastasis occurs in 50 percent of patients with stage II disease.

The factors associated with a favorable prognosis are: 1) an absence of symptoms at the time of detection; 2) age of 19 years or older at diagnosis; 3) small tumor size; 4) minimal invasion; and 5) a tubulocystic pattern. Women without a history of DES exposure have a worse prognosis and a higher rate of distant metastases than women with such a history. These differences do not appear to be due to differences in clinical prognostic factors, such as size or stage, but instead due to other as yet undetermined factors (144).

The 5-year survival rate of patients with tumors of all stages is approximately 80 percent for patients with stage I tumors; it is 93 percent at 5 years and 87 percent at 10 years. When patients are asymptomatic and tumors are detected during the course of an examination because of a history of DES exposure, survival approaches 100 percent. Although most recurrences occur within 3 years, disease-free intervals of up to 19 years have been observed. Compared with squamous cell carcinoma of the vagina and cervix, clear cell adenocarcinoma has a greater tendency to spread beyond the abdominal cavity. Of the initial recurrences of clear cell carcinoma, 36 percent are in the lungs or supraclavicular lymph nodes, in contrast to less than 10 percent at these sites for squamous cell carcinoma (110).

For early-stage disease, radical hysterectomy, vaginectomy, and lymphadenectomy are recommended because there is a higher risk of recurrence with local excision. Radiotherapy is equally effective for early disease, but is generally reserved for advanced-stage disease.

Mesonephric Carcinoma

Only a few cases of carcinoma arising from mesonephric remnants in the vagina have been reported (57,151). *Mesonephric carcinomas* are composed of well-formed tubules lined by atypical, mitotically active, cuboidal to columnar epithelial cells that resemble mesonephric duct remnants. In contrast to clear cell carcinoma, mesonephric carcinoma does not contain clear cells or hobnail cells. Intracellular mucin and glycogen are not present, and the tubules are often surrounded by a basement membrane that can be appreciated with PAS stains. In more poorly differentiated carcinomas, the resemblance to mesonephric duct remnants is less obvious because the predominant architecture is that of crowded solid nests and cords of cells.

OTHER EPITHELIAL TUMORS

Adenosquamous Carcinoma

Adenosquamous carcinomas represent about 2 percent of primary vaginal carcinomas. Of 244 cases of primary epithelial tumors of the vagina, 6 adenosquamous carcinomas were reported in women with a mean age of 55 years (108,121,132). In none of these women was adenosis or endometriosis present; however, the possibility that small foci of adenosis or endometriosis were not sampled or were overgrown by tumor cannot be excluded.

Adenosquamous carcinoma in the lower third of the vagina may arise from minor vestibular glands or Bartholin glands. An origin from mesonephric ducts is unlikely because carcinomas of mesonephric differentiation do not undergo squamous differentiation. A cloacogenic origin has been suggested in view of the similar appearance of some adenosquamous carcinomas to cloacogenic carcinomas of the rectum and anus (108).

Microscopically, adenosquamous carcinomas are composed of both squamous and glandular elements and resemble their counterparts in the cervix. Some are mucoepidermoid carcinomas. Some tumors are locally aggressive (108); one metastasized to the lungs and was fatal within 19 months of diagnosis (132).

Miscellaneous Tumors

A variety of carcinomas have been reported as primary vaginal neoplasms. These include *adenoid basal cell carcinoma* (79), *adenoid cystic carcinoma*, and *neuroendocrine carcinoma* (37). The latter tumor was composed of mucin-secreting goblet cells and small undifferentiated cells,

some of which were positive with argentaffin and argyrophil stains. Widespread metastases developed, and the patient died 1 year after treatment. On rare occasion, *small cell carcinoma* may arise as a primary vaginal tumor, identical in appearance to small cell carcinoma of the cervix. A primary *lymphoepithelioma-like carcinoma* (26) and a *serous carcinoma of the vagina* (109) have also been reported. The latter tumor was highly aggressive, similar to its ovarian and uterine corpus counterparts. As in other sites, undifferentiated carcinomas occur in the vagina. Two cases of primary *Brenner tumor* of the vagina have been described (6).

MESENCHYMAL TUMORS

Mesodermal Stromal Polyp

Mesodermal stromal (fibroepithelial) polyp is also referred to as *pseudosarcoma botryoides* (29). Patients range in age from newborn to 71 years, with most over the age of 20 years. The median age in the largest series was 35 years (85). Nearly one third of the patients are pregnant at the time of diagnosis. Although occasionally presenting with abnormal bleeding, most of the polyps are incidental findings. The majority are single and occur on the lateral wall in the lower third of the vagina.

Mesodermal stromal polyps range in size from 0.5 to 4.0 cm, with a median diameter of 1.7 cm. They are usually polypoid or pedunculated and, on section, gray-white, soft, and rubbery.

Microscopically, they are well circumscribed and composed of edematous fibrous tissue covered by benign squamous epithelium. The edematous fibrous tissue stroma contains numerous dilated blood vessels. Scattered enlarged fibroblasts with plump hyperchromatic or vesicular nuclei and delicate cytoplasmic processes are seen in a background of acellular stroma (fig. 6-13). In approximately half the cases, the fibroblasts are atypical with large, pleomorphic, and often hyperchromatic multiple nuclei. A cambium layer and heterologous elements are not present and mitotic activity is low. Although edema may be present focally, it is not a striking feature. Occasionally, there is marked stromal cellularity and mitotic activity may exceed 10 mitotic figures/10 high-power fields. Similar to the less cellular polyps, these behave in a benign fashion (86).

The pathogenesis of vaginal polyps is not clear. Because approximately a third of the patients are pregnant at the time of diagnosis, it is possible that these lesions are hormone induced. They may represent focal hyperplasia of the subepithelial stromal cells that form a myxoid stromal matrix extending from the endocervix to the vulva in mature women (28). Atypical stromal cells, similar to those seen in mesodermal stromal polyps, are also seen in nasal polyps (19), giant cell cystitis, radiation cystitis, and nodular fasciitis (85). It is likely, therefore, that these cells are reactive in nature.

The importance of recognizing vaginal polyps lies in distinguishing them from sarcoma botryoides. A number of clinical and pathologic features facilitate the differential diagnosis. Vaginal polyps almost always occur in adults, whereas vaginal sarcoma botryoides rarely occurs beyond the age of 8 years. The rare botryoid type sarcoma occurring in teenagers or adults arises higher in the genital tract, most commonly the cervix. Unlike sarcoma botryoides, which grows rapidly, polyps pursue an indolent course (91). Microscopically, in contrast to sarcoma botryoides, vaginal polyps lack a cambium layer, small undifferentiated stromal cells, invasion of the overlying squamous epithelial cells, and rhabdomyoblasts. Vaginal polyps express desmin and actin but not myogenin.

Treatment consists of local excision. Local recurrence is possible if the lesion is incompletely removed. There has been no evidence of malignant behavior.

Leiomyoma

Leiomyomas are the most common mesenchymal tumor of the vagina in adult women (8,148). Women are of reproductive and postmenopausal age groups (19 to 72 years; mean, 44 years). Tumors detected during early pregnancy may enlarge rapidly. Most leiomyomas are asymptomatic, but depending on their size and position, they may be associated with pain, bleeding, dyspareunia, dystocia, and urinary or rectal symptoms. They occur at any level of the vagina and tend to be solitary.

The tumor has the same gross appearance as a uterine leiomyoma. Vaginal leiomyomas are well circumscribed and range in size from 0.5 to 15.0 cm, with a median of 3.0 cm (134).

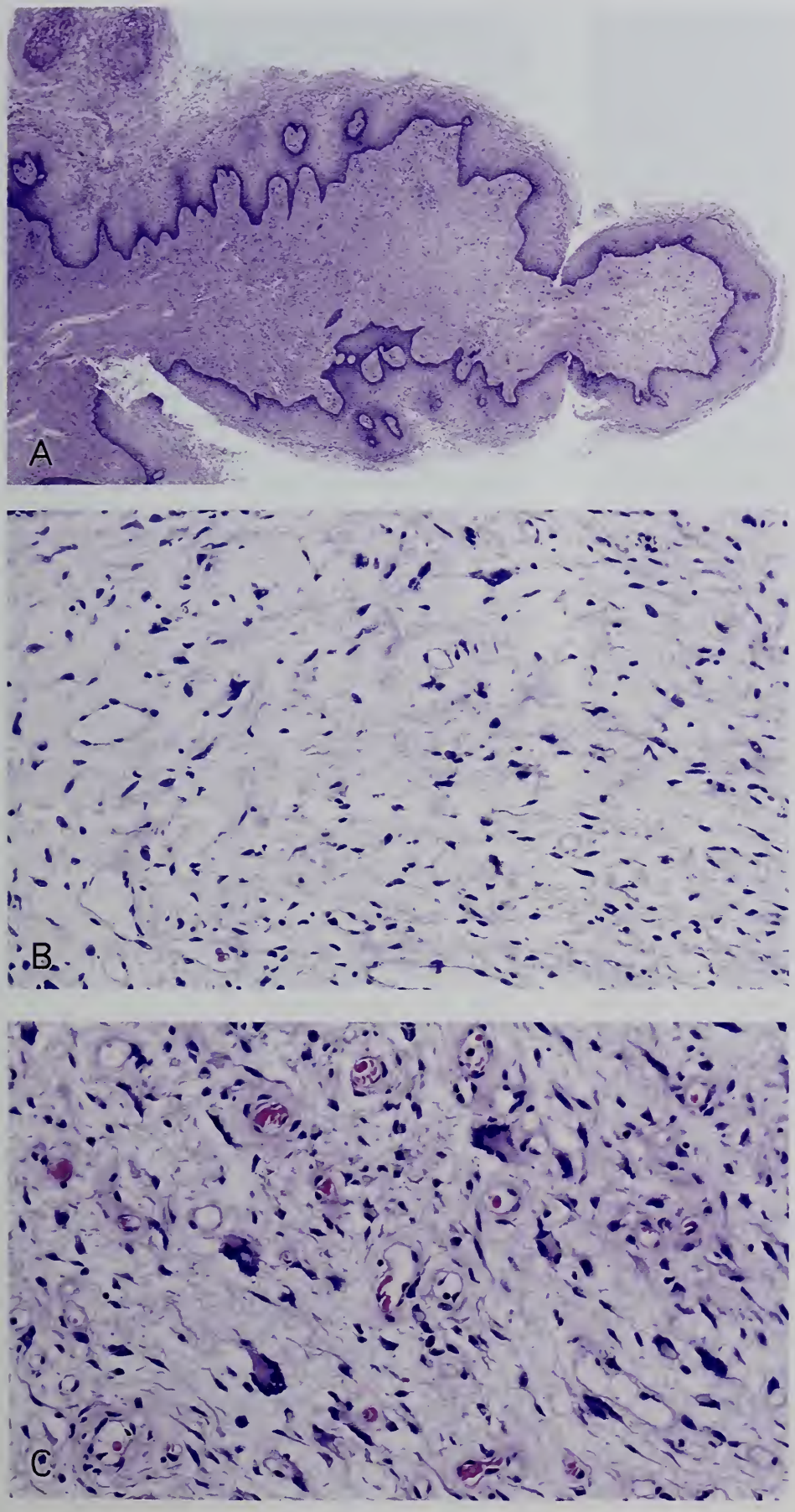


Figure 6-13

MESODERMAL STROMAL POLYP

A: The polyp is covered by normal-appearing squamous mucosa and contains a hypocellular fibrous core.

B: Edematous stroma contains bland spindle cells, some of which exhibit stellate configurations and contain slightly enlarged, smudgy hyperchromatic nuclei.

C: Edematous stroma contains predominantly bland spindle cells and occasional multinucleated stromal cells ("fleurette" cells).

Microscopically, vaginal leiomyomas resemble uterine leiomyomas and may display epithelioid and clear cell patterns (134). Mitotic activity is low or absent. Tumors with 5 or more mitotic figures per 10 high-power fields and moderate or marked cellular atypia are classified as leiomyosarcomas (see Leiomyosarcoma). In one series of 60 smooth muscle tumors of the vagina (134), 33 had no mitotic activity and 18 had 1 to 4 mitotic figures per 10 high-power fields; none of these tumors recurred or metastasized. In pregnancy, increased mitotic activity is observed in some tumors, but in the absence of significant atypia, these tumors should be classified as leiomyomas. Local excision is adequate treatment for vaginal leiomyomas.

Superficial Cervicovaginal Myofibroblastoma

Superficial cervicovaginal myofibroblastoma is a benign polypoid or nodular mesenchymal tumor arising in the superficial lamina propria of the vagina and cervix. It is considered distinctive from mesodermal stromal polyp, aggressive angiomyxoma, angiomyofibroblastoma, and cellular angiofibroma (67). These tumors occur in women 40 to 74 years of age and measure 1.0 to 6.5 cm. They are subepithelial and well circumscribed. They are characterized by bland spindle- and stellate-shaped cells with finely collagenous stroma, occasional myxoid and edematous foci, and moderate to high cellularity with lace-like/sieve-like growth in stromal-rich areas and fascicular growth in cellular areas (fig. 6-14). The tumors uniformly express vimentin, hormone receptors, and desmin; often express CD34; occasionally express alpha-smooth muscle actin and muscle specific actin; and are negative for S-100 protein, epithelial membrane antigen, and keratins. No recurrences or metastases have been seen after local excision.

Rhabdomyoma

Only 20 *vaginal rhabdomyomas* have been recorded (38,119) since the initial report by Ceremsak (13). Patients range in age from 34 to 57 years; mean age is 44 years. Rhabdomyomas are solitary and nodular or polypoid, ranging in diameter from 1 to 11 cm. They may arise anywhere in the vagina, and some protrude into the lumen.

Rhabdomyomas are composed of mature, bland rhabdomyoblasts that are oval or racket-shaped with obvious cross striations. Abundant connective tissue stroma surrounds individual muscle cells (fig. 6-15). Electron microscopy reveals well-organized myofibrils with Z-bands similar to normal striated muscle (42,69).

It is important to distinguish vaginal rhabdomyoma from sarcoma botryoides (embryonal rhabdomyosarcoma), and from the vaginal polyp. Unlike rhabdomyoma, sarcoma botryoides of the vagina occurs in young children and not adults. Rhabdomyoma lacks a cambium layer, is composed of primitive mesenchymal cells, and the rhabdomyoblasts are mature with obvious cross striations. There is no nuclear atypia and mitotic figures are absent. Vaginal polyps have a clinical presentation similar to that of rhabdomyomas but are distinguished microscopically by the absence of striated muscle cells. Rhabdomyomas are benign and are treated by local excision.

Other Benign Mesenchymal Tumors

A variety of benign mesenchymal neoplasms of histiocytic, neurogenic, and vascular origin have been reported. These consist largely of single case reports. The tumors have the same histologic appearance and clinical behavior as those in other sites, where they occur more commonly, and are therefore not described in detail. The tumors include *granular cell tumor* (40,64), *neurofibroma* (24,41), *schwannoma* (30), *benign triton tumor* (5), *paraganglioma* (98), *glomus tumor* (128), and *hemangioma* (43).

Leiomyosarcoma

Smooth muscle tumors with 5 or more mitotic figures per 10 high-power fields that exhibit moderate or marked cytologic atypia are classified as *leiomyosarcomas* (134). The behavior of smooth muscle tumors with more than 5 mitotic figures per 10 high-power fields but lacking atypia is unknown. Because older reports in the literature have used variable criteria, it is difficult to be certain of the prevalence of these tumors. Peters et al. (95), in reviewing the literature, found that 41 of 68 vaginal sarcomas (60 percent) in adults were leiomyosarcomas. The patients ranged in age from 25 to 86 years. The most common presenting symptom was bleeding.

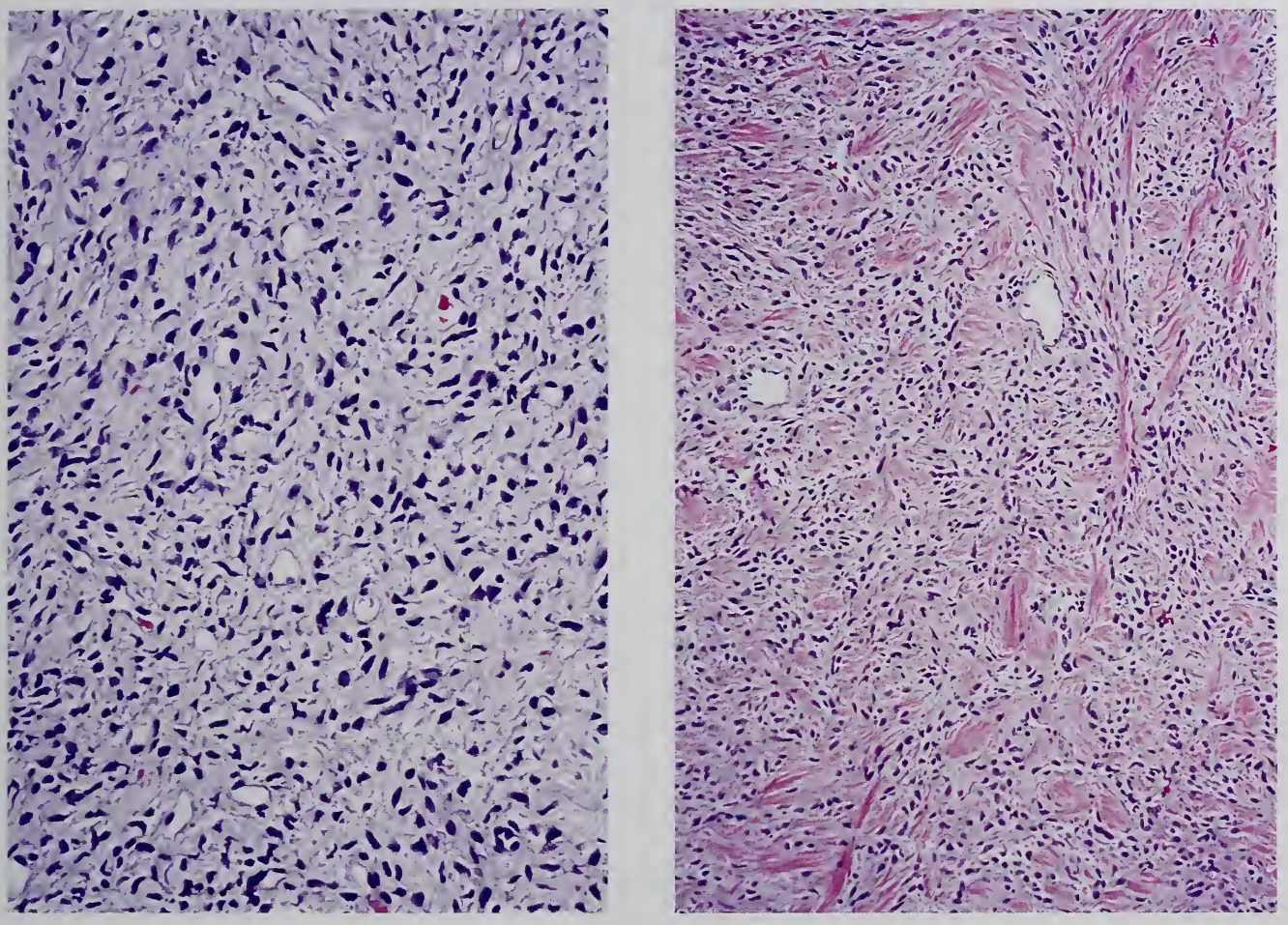


Figure 6-14

SUPERFICIAL CERVICOVAGINAL MYOFIBROBLASTOMA

Left: The tumor is moderately cellular and composed of a uniform population of spindle cells within a homogeneous collagenous stroma containing occasional small vessels.

Right: Dense collagen bundles are intimately admixed with a moderately cellular, uniform spindle cell population.

On gross examination, leiomyosarcomas are usually bulky, ranging in size from 3 to 10 cm (23). Microscopically, they are identical to leiomyosarcomas elsewhere.

Leiomyosarcomas invade locally and metastasize via the bloodstream to distant sites. In one review, the 5-year survival rate was 36 percent (95). Partial vaginectomy may suffice for small neoplasms, but because of the difficulty in obtaining adequate margins between the vagina and bladder and rectum, pelvic exenteration may be necessary for large tumors.

Sarcoma Botryoides (Embryonal Rhabdomyosarcoma)

Definition. *Embryonal rhabdomyosarcoma* arising in organs with a mucosal lining has the appearance of a bunch of grapes, and hence the term "botryoid" has been used. In the vagina, the tumor has distinctive pathologic features, justifying the term *sarcoma botryoides*.

General Features. Sarcoma botryoides, although rare, is the most common vaginal sarcoma (23). It occurs almost exclusively in children and infants. Nearly 90 percent of tumors are encountered in children less than 5 years old; the mean age is 2.5 years (34). Four cases have been reported in women after puberty; the oldest patient thus far reported was 63 years old (123).

The histogenesis is not known. The tumor develops from mesenchymal cells in the lamina propria that differentiate to some degree into striated muscle.

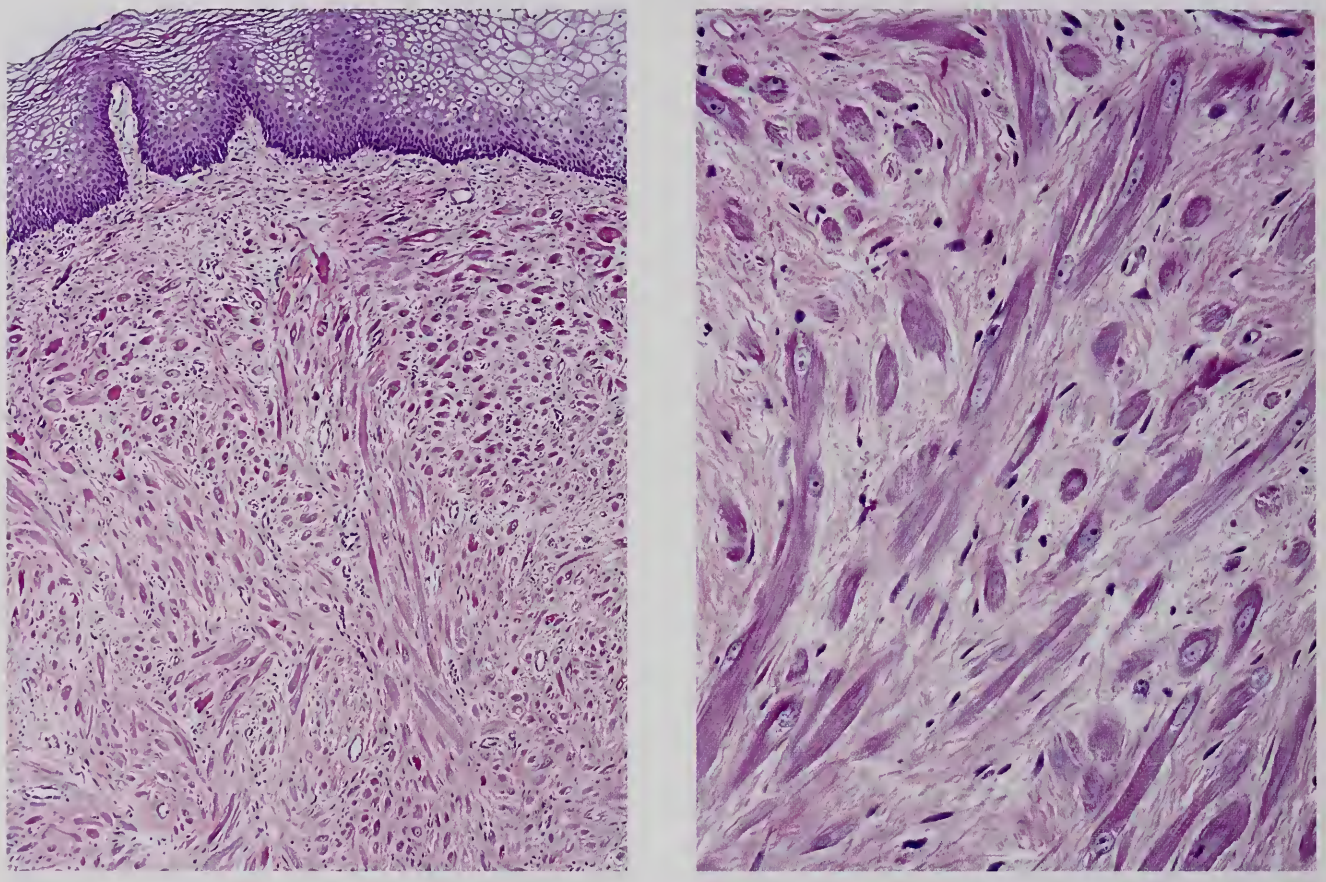


Figure 6-15

RHABDOMYOMA

Left: The lesion is situated in the subepithelial stroma and contains elongated, densely eosinophilic fibrils, which on higher magnification are mature rhabdomyoblasts (right).

Right: The lesion is composed of elongated mature rhabdomyoblasts, some of which have evident cross striations.

Clinical Features. Typically, sarcoma botryoides presents as a mass filling the vagina and often protruding from it. Small lesions present as translucent nodules. The overlying mucosa may be intact or ulcerated. Patients may have bleeding and discharge. Bladder and rectal symptoms are associated with local extension of the tumor. Rarely, a patient presents with metastasis to the lungs or bone (46). The tumor arises anywhere in the vagina but most frequently involves the anterior wall.

Gross Findings. The tumor is pedunculated or sessile and is composed of multiple polypoid masses, each of which measures 3 to 4 cm. The entire tumor ranges from 0.2 to 15.0 cm in greatest dimension. Sectioning reveals gray, translucent, myxoid tissue with areas of hemorrhage.

Microscopic Findings. The tumor is covered by an attenuated layer of squamous epithelium, beneath which is a compact, highly cellular cambium layer of small, round to spindle-shaped, undifferentiated cells with hyperchromatic nuclei and scant cytoplasm (89). These cells occasionally invade the overlying squamous epithelium. Beneath the cambium layer is a more sparsely cellular region containing a similar population of cells more widely separated by edematous or myxomatous stroma. In this region, and in the cambium layer, rhabdomyoblasts are recognized as round, racquet-shaped or strap cells, with prominent eosinophilic cytoplasm. Cross striations may be difficult to identify but do not need to be identified to make the diagnosis. The neoplastic cells tend to condense around blood vessels. Mitotic activity is generally brisk. Heterologous elements such as bone and cartilage are not present (fig. 6-16).

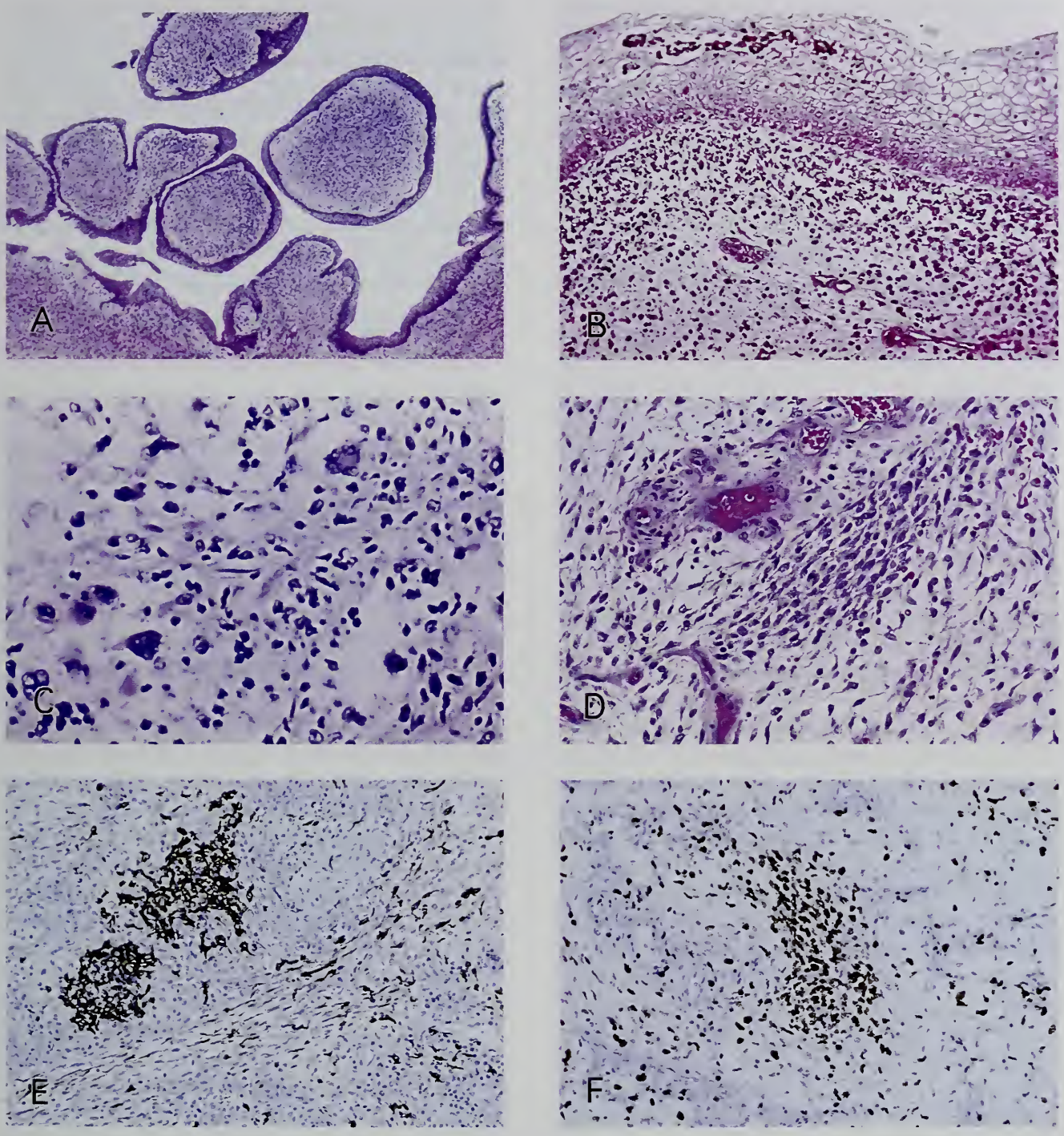


Figure 6-16

SARCOMA BOTRYOIDES (EMBRYONAL RHABDOMYOSARCOMA)

A: The tumor is polypoid and composed of a cellular stromal proliferation beneath normal squamous mucosa.

B: The cellular cambium layer is evident immediately beneath the squamous epithelium.

C: Edematous stroma contains predominantly atypical spindle cells with minimal cytoplasm and occasional multinucleated cells with eosinophilic cytoplasm, simulating a mesodermal stromal polyp with fleurette cells.

D: Predominantly hypocellular stroma contains hypercellular aggregates of atypical spindle cells with fine eosinophilic cytoplasmic processes. Mitotic figures are typically found in these cellular foci.

E: There is immunohistochemical evidence of muscle differentiation, shown by the expression of desmin.

F: The tumor has an elevated Ki-67 proliferation index, which is most notable in the hypercellular aggregates, in which virtually all the tumor nuclei are positive.

Immunohistochemical Findings. Immunohistochemistry is helpful in identifying striated muscle differentiation that is not evident by conventional light microscopy. Although not specific for striated muscle, commercially available desmin and muscle-specific actin are far more sensitive in detecting muscle (smooth and striated) differentiation than myoglobin, which is specific for striated muscle; however, muscle-specific actin antibody is not specific for muscle because it may react with myoepithelial cells and myofibroblasts as well. Myogenin, a transcription factor that is expressed in striated muscle, is useful for confirming the presence of rhabdomyoblasts among the desmin-positive cells. The tumor has a notably elevated proliferation index as assessed by immunohistochemical expression of Ki-67.

Differential Diagnosis. Sarcoma botryoides should be distinguished from benign vaginal polyps, rhabdomyomas, and müllerian papillomas. In contrast to sarcoma botryoides, which is covered by squamous epithelium and contains hyperchromatic, undifferentiated spindle cells in the stroma, müllerian papilloma is covered by columnar epithelium and the stroma is bland. Müllerian papilloma also lacks a cambium layer. The diagnosis of sarcoma botryoides must be considered when dealing with a polypoid lesion of the vagina in a child. Attention should be directed to the small undifferentiated cells under high magnification because they may be incorrectly interpreted as inflammatory cells under low magnification.

Treatment and Prognosis. The tumor grows primarily by local invasion. Depending on its location in the vagina, it invades anteriorly into the bladder or posteriorly into the rectum. Distant metastasis occurs later in the course of the disease and involves inguinal, pelvic, retroperitoneal, and mediastinal lymph nodes; lung; liver; pericardium; kidney; and bone.

Sarcoma botryoides is a very aggressive tumor. Pelvic exenteration was advocated in the past because of the high local recurrence rate. More recently, extended surgery combined with chemotherapy has led to a dramatic improvement in survival. This surgery is less radical and spares the bladder and rectum. In a study in which vincristine, actinomycin D, and cyclophosphamide were used immediately after a biopsy, and followed by a hysterectomy and partial or total vaginectomy, there were only 3 deaths among 28 patients (46).

Endometrioid Stromal Sarcoma

Both low-grade and high-grade (undifferentiated) *endometrioid stromal sarcomas* have been encountered in the vagina, sometimes arising from endometriosis (95). Before concluding that such a neoplasm is primary in the vagina, an origin in the uterus should be excluded.

Other Malignant Mesenchymal Tumors

Malignant schwannoma (23), *fibrosarcoma* (92), *malignant fibrous histiocytoma* (145), *angiosarcoma* (102), *alveolar soft-part sarcoma* (81), *alveolar rhabdomyosarcoma*, *extraosseous Ewing sarcoma* (139), and unclassifiable sarcomas have all been described in the vagina, but they do not exhibit unique clinical or pathologic features in this region.

MIXED EPITHELIAL AND MESENCHYMAL TUMORS

Mixed Tumor

Mixed tumor of the vagina is composed of epithelial and mesenchymal cells, and, to some extent, simulates a mixed tumor (pleomorphic adenoma) of the salivary gland. The origin may be from müllerian or urogenital-derived epithelium. Its frequent location in the hymenal region also suggests an origin from minor or major vestibular glands. Most reports of this unusual neoplasm have been individual cases (12,14), except for two larger series (11,126). The patients range in age from 20 to 69 years, with a mean age of 41 years. The tumors arise on the lateral, posterior, and anterior vaginal walls, but have a predilection for the hymenal area. They range in size from 1.5 to 6.0 cm and are usually located just beneath the mucosal surface, presenting as an asymptomatic mass.

On gross examination, mixed tumors are discrete, gray, and soft masses. They are often gelatinous, slick, and translucent. Microscopically, a mixture of epithelial and mesenchymal tissues is observed. The bulk of the tumor is composed of nondescript spindle cells, probably representing fibroblasts (fig. 6-17) (126). These cells are arranged in bundles but characteristically display

a whorled pattern. The cells have little if any cytologic atypia, and mitotic figures are uncommon. Nests of glycogenated stratified squamous epithelium, which may demonstrate pearl formation, may be dispersed throughout the stroma. Scattered glands lined by mucinous epithelium may also be present. The glandular epithelium merges with the squamous epithelium.

Immunohistochemical stains show intense staining for cytokeratin in the spindle cells. In addition, there is positive staining for smooth muscle actin, estrogen receptor (ER), and progesterone receptor (PR). The immunohistochemical and ultrastructural findings support epithelial differentiation in these tumors, which has prompted some investigators to propose that these lesions be termed "vaginal spindle cell epitheliomas" (11). Recurrence at the original site of surgery has been reported after local excision in three cases (11), but no tumor has metastasized.

Mixed Tumor Resembling Synovial Sarcoma

Neoplasms that have a biphasic pattern have been reported to arise in the lateral fornix of the vagina (90,122). Regarded as *mixed tumors resembling synovial sarcoma*, the tumors are composed predominantly of gland-like structures. The glands are lined by flattened epithelial cells that abut spindle-shaped cells, suggesting sarcomatous differentiation. The biphasic differentiation suggests a synovial sarcoma, but the neoplasm does not resemble the typical synovial sarcoma arising in soft tissue. In one study, electron microscopic examination demonstrated slender, long microvilli protruding into the acinar lumens, reminiscent of synovial cells (90). In another study, although the light and ultrastructural findings were suggestive of synovial sarcoma, electron microscopy did not reveal the telolysomes seen in synovial sarcoma (122). Because the tumor was closely associated with mesonephric remnants and was located in the lateral fornix, the authors concluded that it probably arose from mesonephric nests.

Adenosarcoma

The vagina may be the site of recurrence of a uterine adenosarcoma or the site of a primary *adenosarcoma*. Adenosarcoma of the vagina has gross features similar to those of sarcoma botryoides, but is microscopically similar to adenosarcoma arising in the uterine corpus. The leaf-like pattern, characterized by clefts lined by bland epithelium overlying a hypercellular spindle-cell stroma, is typical.

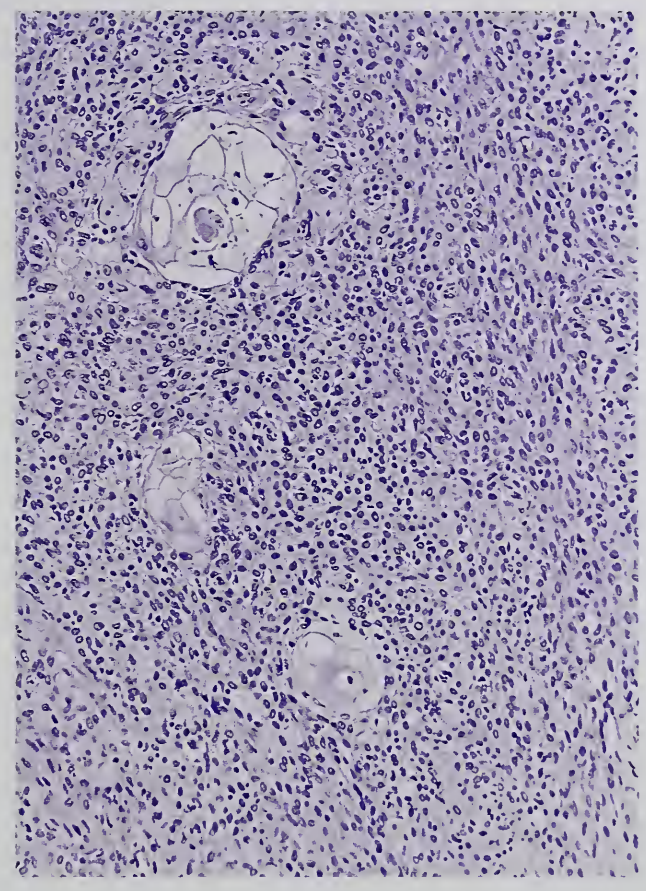


Figure 6-17

MIXED TUMOR

The tumor is cellular and composed of aggregates of monotonous spindled to epithelioid cells with a few islands of squamous epithelium.

Malignant Mixed Mesodermal Tumor (Carcinosarcoma)

There have been seven reports of primary *malignant mixed mesodermal tumor (carcinosarcoma)* of the vagina (95). In four there was a history of prior radiation. The histologic appearance is similar to that of mixed mesodermal tumors of the uterine corpus.

MISCELLANEOUS TUMORS

Melanocytic Nevus

Melanocytic nevi identical to those on the skin occur in the vagina.

Blue Nevus

Blue nevus occurs rarely in the vagina (135); it is more common in the cervix and vulva. The histologic appearance is similar to that of its counterpart in the skin.

Malignant Melanoma

General Features. Primary *malignant melanoma* of the vagina accounts for less than 0.3 percent of all melanomas and less than 3.0 percent of malignant tumors of the vagina (70): approximately 115 cases have been reported (107). The tumor is thought to arise from melanocytes, which are present in the vaginal epithelium in 3 percent of normal women (82). These tumors occur predominantly in white postmenopausal women of a mean age of 62 years. The most common symptom is vaginal bleeding. Melanoma may occur anywhere in the vagina, but most often involves the lower third (107).

Gross Findings. Melanomas project above the vaginal surface and are blue or black and soft. They are usually ulcerated (84). They range in size from 0.5 cm to a large tumor involving the entire vaginal wall (16).

Microscopic Findings. Vaginal melanomas do not have a distinctive pattern. The tumor cells are usually pigmented, but may be amelanotic. The tumor may be composed predominantly of small or spindle-shaped cells (fig. 6-18). Cellular pleomorphism may be marked and mitotic activity is often high. Junctional activity is almost always demonstrated and frequently there is lateral junctional spread of tumor cells. Junctional activity identifies the vagina as the primary site of the tumor. Melanocytes in the vagina near the melanoma are often angulated and atypical, reminiscent of those in lentiginous melanoma of the skin (16). Their presence is useful in distinguishing melanoma from a benign nevus.

Because the vagina does not have a papillary and reticular dermis, Chung et al. (16) modified Clark levels and Breslow thickness measurements for vaginal melanoma. Among 31 patients in whom the level of invasion could be determined, only 4 had tumors that invaded less than 2 mm (107). The deep invasion of these tumors at the time of diagnosis probably accounts for the poor prognosis of the patients. Accordingly, the depth of invasion in millimeters should be indicated in order to provide an estimate of prognosis.

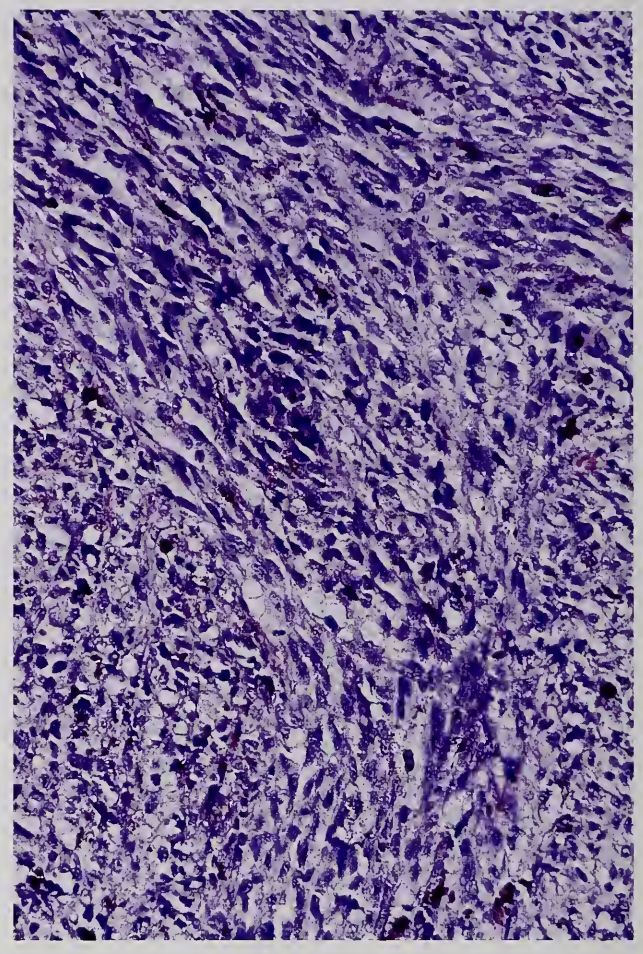


Figure 6-18

MALIGNANT MELANOMA

The hypercellular tumor is composed of atypical spindled cells, some of which contain fine dark brown pigment.

Differential Diagnosis. As in other sites, it is important to maintain a high index of suspicion for melanoma when faced with a poorly differentiated spindle or epithelioid cell neoplasm that is difficult to classify. Because of their rarity in the vagina and the frequent associated ulceration with loss of areas of junctional activity, melanomas may be confused with lymphomas, sarcomas, or carcinomas. Immunohistochemical stains for S-100 protein, melanoma-specific antigen (HMB45), melan-A, cytokeratins, leukocyte common antigen (CD45), and desmin are very useful in the differential diagnosis, with melanomas usually expressing one or more of the melanoma markers (S-100 protein, HMB45, Melan-A) and lacking the other markers.

Treatment and Prognosis. The prognosis is much worse than for patients with cutaneous melanomas: the 5-year crude survival rate ranges from 5 to 20 percent. Similar to cutaneous melanomas, vaginal melanomas may recur long after 5 years. The prognosis appears to be influenced by tumor size, with lesions greater than 3 cm conferring a significantly worse prognosis (107). Although patients with tumors that invade 1 mm or less appear to have a better survival rate, the number of cases is too few to draw firm conclusions. Age, mitotic count, stage, and location of the lesion do not influence survival. Most recent reports recommend conservative management with radical procedures reserved for palliation (80), but one study reported an improved outcome for tumors less than 10 cm^2 with radical therapy (exenterative surgery, radical hysterectomy, vaginectomy, and lymph node dissection) as opposed to conservative therapy (radiotherapy, chemotherapy, wide local excision, simple hysterectomy, or a combination of any of these approaches) (137).

Yolk Sac Tumor

Yolk sac tumors (endodermal sinus tumors) resembling those found in the ovary and testis arise in the vagina. Of those originating in the lower genital tract, most are in the vagina, with an occasional example in the cervix or vulva (18). They may arise from displaced germ cells arrested during embryonic migration from the yolk sac to the gonadal ridge or from aberrant differentiation of somatic cells (150).

Vaginal yolk sac tumors have been reported exclusively in children 3 years of age or younger. The patients present with bleeding or discharge and have polypoid or sessile tumors 1 to 5 cm in greatest dimension. Gross examination discloses a gray-white, soft, friable tumor that may be focally hemorrhagic. Microscopically, the tumor displays the various patterns encountered in the more common ovarian yolk sac tumor, the most frequent being the microcystic or reticular pattern. Schiller-Duval bodies and hyaline droplets are characteristic. As in the ovary, immunohistochemical reactions for alpha-1-fetoprotein, alpha-1-antitrypsin, and albumin are typically positive (150).

In the past, the outlook was grave, with the majority of patients dying despite radical surgery. Since 1970, the use of multiagent chemotherapy, usually consisting of vincristine, actinomycin D, and cyclophosphamide (VAC), combined with surgery, has resulted in an excellent cure rate (20). A novel approach utilizing primary chemotherapy (VAC) followed by local excision without pelvic irradiation has resulted in long-term cure. The latter approach has the added advantage of preserving reproductive and sexual functions (3).

Mature Cystic Teratoma

Five *teratomas* of the vagina and an unusual ectopia composed exclusively of thyroid and parathyroid tissue have been reported (65). The five teratomas were all mature and cystic, lined by squamous epithelium, and contained hair and sebaceous material; neural tissue and teeth were found in three of these. Primary immature (malignant) teratomas, embryonal carcinomas, and dysgerminomas have not been reported, to our knowledge, in the vagina.

Adenomatoid Tumor

A primary vaginal *adenomatoid tumor* has been reported (71). The microscopic appearance was that of a typical adenomatoid tumor.

Villous Adenoma

A *villous adenoma* of the vagina in a 59-year-old woman has been reported (32), and we have seen additional examples. The adenoma presents as a polypoid lesion. The lesion is microscopically identical to villous adenoma of the large intestine (fig. 6-19). Because the vagina is, at least in part, of urogenital sinus origin, it is likely that these tumors arise from cells with the potential of endodermal differentiation.

MALIGNANT LYMPHOMA AND OTHER LYMPHOHISTIOCYTIC LESIONS

Malignant lymphoma may involve the vagina as part of systemic disease or local disease (15,138). In the lower genital tract, lymphoma more often involves the cervix, which is discussed in greater detail in chapter 5. *Plasmacytomas* may be primary in the vagina (27). Of the five reported cases in this location, one recurred locally, and another with local recurrence showed multiple bone metastases. *Eosinophilic granuloma* has also been described in the vagina (152) This lesion may be associated with some or all of the other features of a

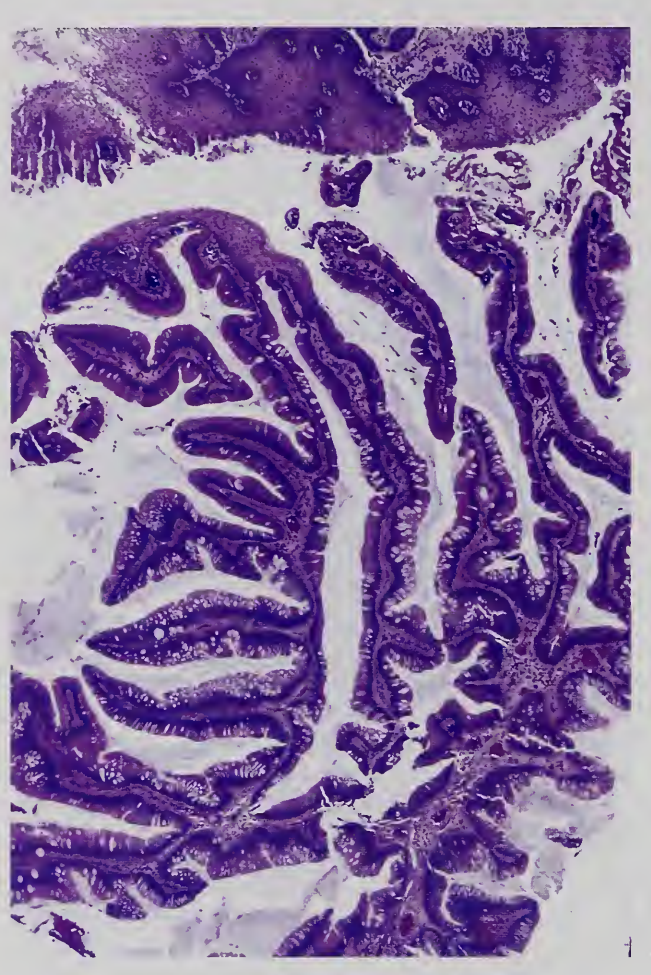


Figure 6-19

VILLOUS ADENOMA

A villoglandular proliferation lined by mucinous intestinal type epithelium with goblet cells simulates a villous mucinous adenoma of the gastrointestinal tract.

syndrome characterized by diabetes insipidus, pituitary hypofunction, and abnormal chest and skeletal films.

Primitive Neuroectodermal Tumor

Extraosseous tumors resembling *primitive neuroectodermal tumor* (*Ewing sarcoma*) have been described in the cervix and uterine corpus and two have been reported in the vagina (39).

SECONDARY TUMORS

Neoplasms of the vagina are much more often metastatic than primary. Spread to the vagina is either by direct extension, vascular or lymphatic embolization, or infrequently, direct implantation. In a review of 355 carcinomas involving the vagina, Fu and Reagan (35) reported that 84 percent were secondary and 16 percent primary. Among secondary squamous carcinomas, the most common primary site was the cervix (79 percent), followed by the vulva (17 percent). Among adenocarcinomas, 92 percent were secondary. The most frequent primary site was the endometrium (32 percent), followed by the rectum and colon (26 percent), and ovary (17 percent). Less commonly encountered neoplasms metastatic to the vagina are transitional cell carcinoma from the urinary bladder and urethra, renal cell carcinoma, uterine mixed mesodermal tumors, malignant melanoma (fig. 6-20), breast carcinoma (fig. 6-21), choriocarcinoma, epithelioid trophoblastic tumor, carcinoma of the Bartholin gland, and cloacogenic carcinoma of the anus.

TUMOR-LIKE LESIONS

Postoperative Spindle Cell Nodule

This benign spindle cell lesion develops just beneath the surface squamous epithelium and is characteristically discovered shortly after a surgical procedure such as hysterectomy (105). *Postoperative spindle cell nodule* is composed of actively proliferating plump spindle cells arranged in intersecting fascicles that infiltrate the adjacent tissue in irregular tongues. A storiform pattern is not evident. The cells contain abundant eosinophilic or amphophilic cytoplasm. The nuclei are oval and uniform, with delicate chromatin and one or two distinct nucleoli (fig. 6-22). Mitotic figures range from 1 to 25 per 10 high-power fields. A delicate network of blood vessels is present within the lesion, and there is typically ulceration of the overlying epithelium accompanied by an acute inflammatory infiltrate. The proliferating cells are mostly fibroblasts and myofibroblasts, or smooth muscle cells in a vascular matrix. Similar to granulation tissue, these lesions only rarely recur despite incomplete excision. Postoperative spindle cell nodules are most often confused with leiomyosarcoma, but in contrast to the latter, they are smaller, have relatively uniform nuclei with delicate chromatin and one or two prominent nucleoli, and follow a recent surgical procedure.

Other reactive sarcoma-like processes that have been described in the vagina are *postoperative fibrohistiocytic proliferation (reparative*

Figure 6-20

METASTATIC MALIGNANT MELANOMA

A cellular, pigmented spindle cell tumor is present within the stroma beneath normal squamous mucosa, suggesting metastatic rather than primary melanoma (primary site was the cervix).

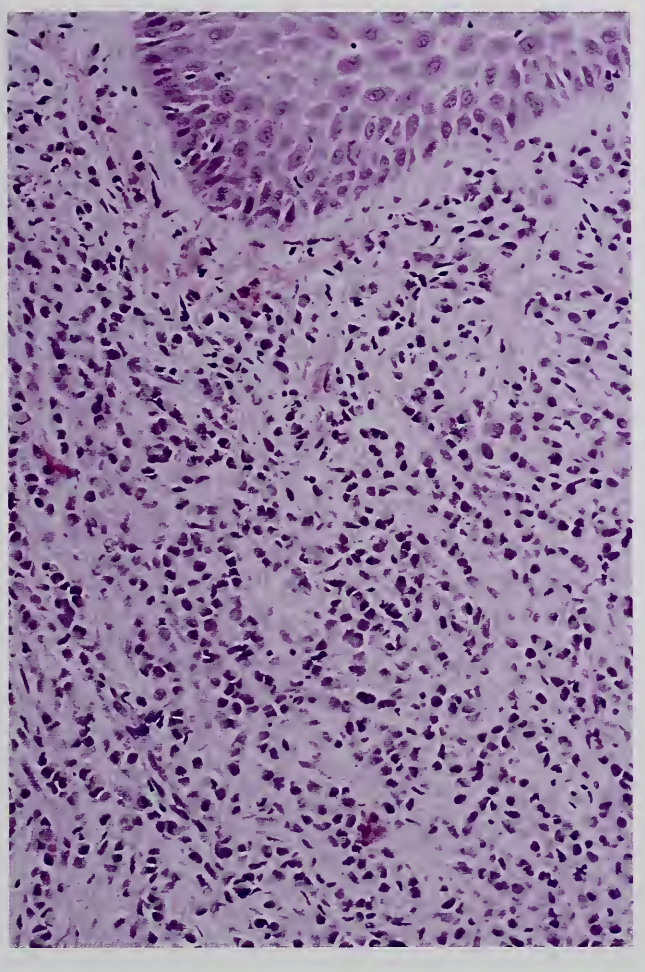


Figure 6-21

METASTATIC BREAST CARCINOMA

The stroma is infiltrated by small epithelioid cells with minimal cytoplasm, which are aligned in single file fashion to form cords, consistent with metastatic lobular breast carcinoma.

granuloma) (127) and *nodular fasciitis* (1). The former lesion has a storiform pattern and contains foamy histiocytes and foreign-body giant cells. It may be related to the spindle cell nodule, differing in its appearance because of a longer time interval between the operation and the diagnosis. In contrast to the postoperative spindle cell nodule, nodular fasciitis is composed of more densely collagenized, less vascular tissue; is associated with local nonsurgical trauma rather than a surgical procedure; and usually arises in the subcutaneous tissue of an extremity rather than in mucosal locations.

Vault Granulation Tissue

Granulation tissue often develops at the vaginal cuff after hysterectomy. Plump fibroblasts and numerous capillaries, typically with an acute and chronic inflammatory infiltrate, are characteristic.

Prolapsed Fallopian Tube

After hysterectomy, typically vaginal hysterectomy, a portion of the fallopian tube may prolapse through the vaginal cuff. Clinically, *prolapsed fallopian tube* is exquisitely tender on palpation and may be associated with dyspareunia. On gross examination, the prolapsed tube may appear as a red granular polypoid mass. Microscopically, it is usually not difficult to recognize the architecture of the fallopian tube, although it usually is partially obscured by granulation tissue and inflammation (fig. 6-23) (125). Prolapsed tube should not be confused

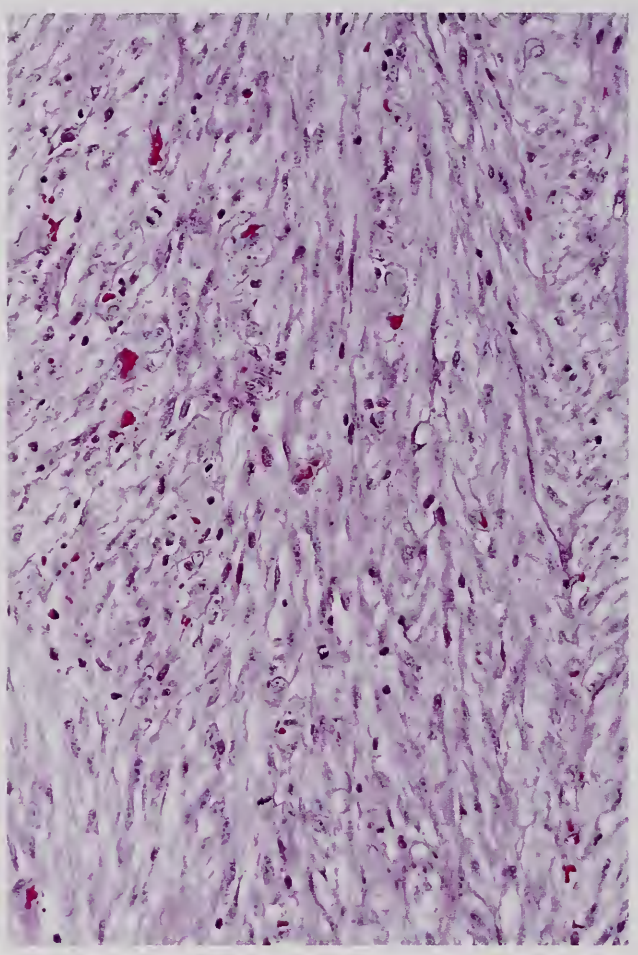


Figure 6-22

POSTOPERATIVE SPINDLE CELL NODULE

Spindle cells arranged in fascicles have eosinophilic cytoplasm and uniform nuclei with occasional mitotic figures.

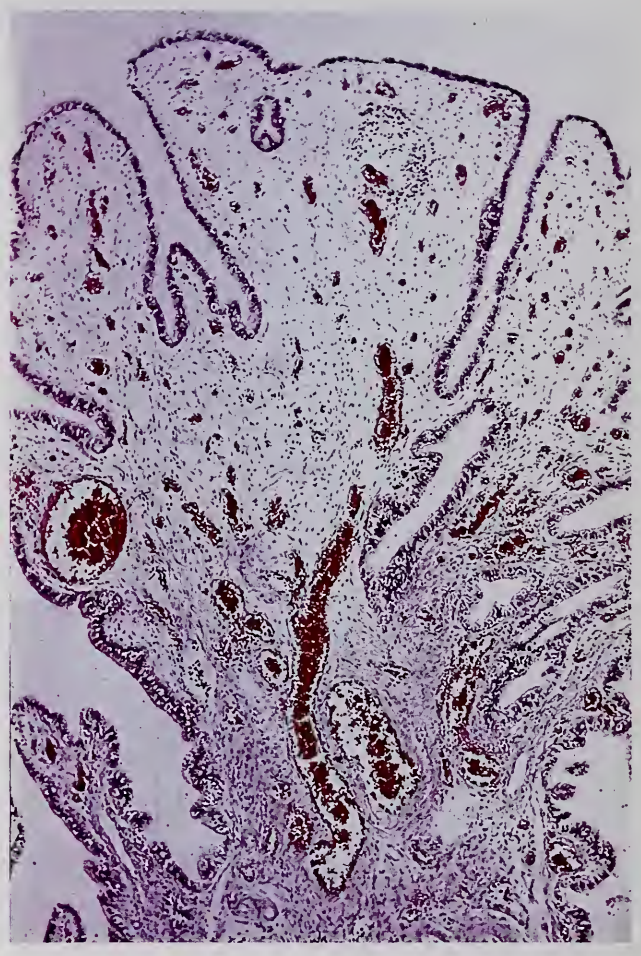


Figure 6-23

PROLAPSED FALLOPIAN TUBE

The papillary structure is composed of edematous plicae lined by tubal type epithelium.

with adenosis, endometriosis, or papillary adenocarcinoma. The location of the lesion, history of prior hysterectomy, architecture, and recognition of tubal epithelial cell types facilitate the diagnosis.

Malakoplakia

Malakoplakia, a chronic inflammatory disease associated with a spectrum of bacterial infections, can occur in the vagina and mimic a variety of infectious, inflammatory, and malignant diseases (63). Over 40 cases have been reported in the vagina. *Escherichia coli* is the most common, and often the only, organism isolated from patients with malakoplakia. Other organisms either associated with or without *E. coli* may be identified. The presence of a mononuclear cell infiltrate and Michaelis-Gutmann bodies establishes the diagnosis.

Lymphoma-Like Lesion

Lymphoma-like lesions are similar to their counterparts in the cervix.

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7 TUMORS OF THE VULVA

SQUAMOUS LESIONS

Squamous Papilloma (Vestibular Papilloma, Micropapillomatosis Labialis)

Squamous (vestibular) papilloma is a benign papillary lesion that characteristically occurs within the vulvar vestibule and is composed of a delicate fibrovascular connective tissue core covered by squamous epithelium.

Squamous papillomas may be less than 0.1 cm in length and rarely exceed 0.5 cm. They are solitary or multiple, and when occurring in clusters, are referred to as *squamous papillomatosis (micropapillomatosis labialis)*. They are identified in approximately one quarter of the women presenting to a colposcopy clinic and may be considered a normal anatomic variant in most cases (116). Patients are asymptomatic, but may present with pruritus.

Squamous papillomas are soft and fleshy. Microscopically, they are covered either by nonkeratinized epithelium, which may be glycogen rich in women of reproductive age, or slightly keratinized epithelium (fig. 7-1). They lack features of human papillomavirus (HPV) infection such as koilocytosis and parabasal cell proliferation. Molecular biological analysis rarely detects HPV DNA sequences in squamous papillomas (28,333).

The differential diagnosis includes condyloma acuminatum, fibroepithelial polyp, and hymenal tags. In contrast to condyloma, squamous papilloma has no or only a thin keratin layer, lacks koilocytosis, usually does not contain HPV, and does not express MIB-1 in the upper two thirds of the epithelium (330). In addition, it typically has a central fibrovascular core and does not show the marked degree of arborization characteristic of condyloma acuminatum. Fibroepithelial polyps have a thick fibrovascular stalk and are typically keratinized.

No treatment is required if the lesions do not cause symptoms. Local ablation by excisional biopsy, topical administration of trichloroacetic acid, and superficial laser ablation are used to manage symptomatic lesions.

Fibroepithelial Polyp

Fibroepithelial polyp is a benign polypoid mass with a prominent fibrovascular core covered by keratinized squamous epithelium (fig. 7-2). There are two morphologic types: one is predominantly epithelial and one is primarily stromal.

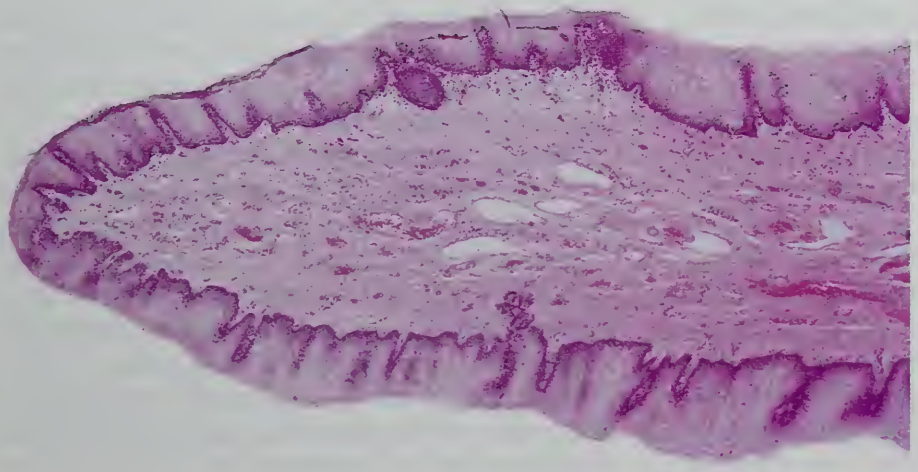


Figure 7-1

SQUAMOUS PAPILLOMA

The thin fibrovascular stalk of the papilloma has overlying glycogen-rich stratified squamous mucosa.

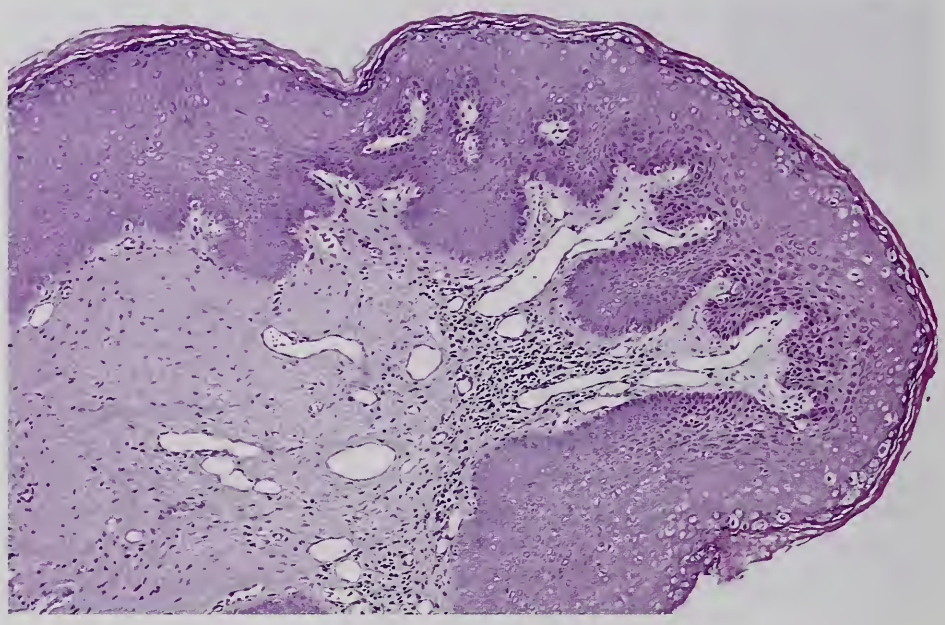


Figure 7-2

FIBROEPITHELIAL POLYP

The polyp has a broad fibrovascular stalk. The surface epithelium has some acanthosis and is hyperkeratotic.

Fibroepithelial polyp is rare on the vulva. It is usually solitary and ranges from 1 to 10 cm in diameter. The larger ones are more likely to be pedunculated and may resemble condyloma acuminatum. The lesion is soft and fleshy, with a prominent fibrovascular stromal component. The epithelium on the surface ranges from highly papillary and acanthotic with hyperkeratosis to thin and atrophic (330).

The differential diagnosis includes condyloma acuminatum, neurofibroma, aggressive angiomyxoma, leiomyoma, and various polypoid soft tissue tumors. In contrast to vestibular papilloma, fibroepithelial polyp occurs on the hair-bearing skin of the vulva. Unlike condylomas, fibroepithelial polyps do not display koilocytosis or contain HPV as demonstrated by in situ hybridization or polymerase chain reaction (PCR) (110). They do not express MIB-1 in the upper two thirds of the epithelium (330) and they lack the complex branching architecture often seen in condyloma. Neurofibromas are more cellular and exhibit S-100 protein immunoreactivity. The aggressive angiomyxoma is deeper, infiltrative, and less polypoid. It also has a more prominent vascular component with muscular arteries scattered throughout. Leiomyomas are more cellular and are composed of smooth muscle cells that are immunoreactive for desmin.

The treatment of fibroepithelial polyp is local excision.

Condyloma Acuminatum

Definition. *Condyloma acuminatum (condylomata)* is a verrucous lesion characterized by acanthosis and elongation and thickening of the rete ridges. Cytopathic effects (koilocytosis) caused by HPV infection are usually displayed.

General Features. The frequency of vulvar condylomata acuminata varies considerably with the population under study and has a frequency generally exceeding 1 percent. Condylomata are usually multiple and commonly involve the vulvar vestibule, medial aspects of the labia majora, and hair-bearing skin and perianal area. Because small lesions may be difficult to detect on clinical examination, the use of 3 to 5 percent topical acetic acid and examination with magnification are usually helpful.

Gross Findings. Condylomata are typically verrucous, papillary, or sessile, but may appear as red, granular areas that turn white after the application of acetic acid.

Microscopic Findings. Although koilocytosis in the upper third of the epithelium is considered pathognomonic, some condylomata lack this feature (fig. 7-3). Often, additional deeper sections disclose focal areas of koilocytosis. When koilocytosis cannot be found, other ancillary findings such as acanthosis, parakeratosis, dyskeratosis, hyperkeratosis, and crowding of parabasal cells assist in the diagnosis of an exophytic papillary lesion (fig. 7-3). The complex

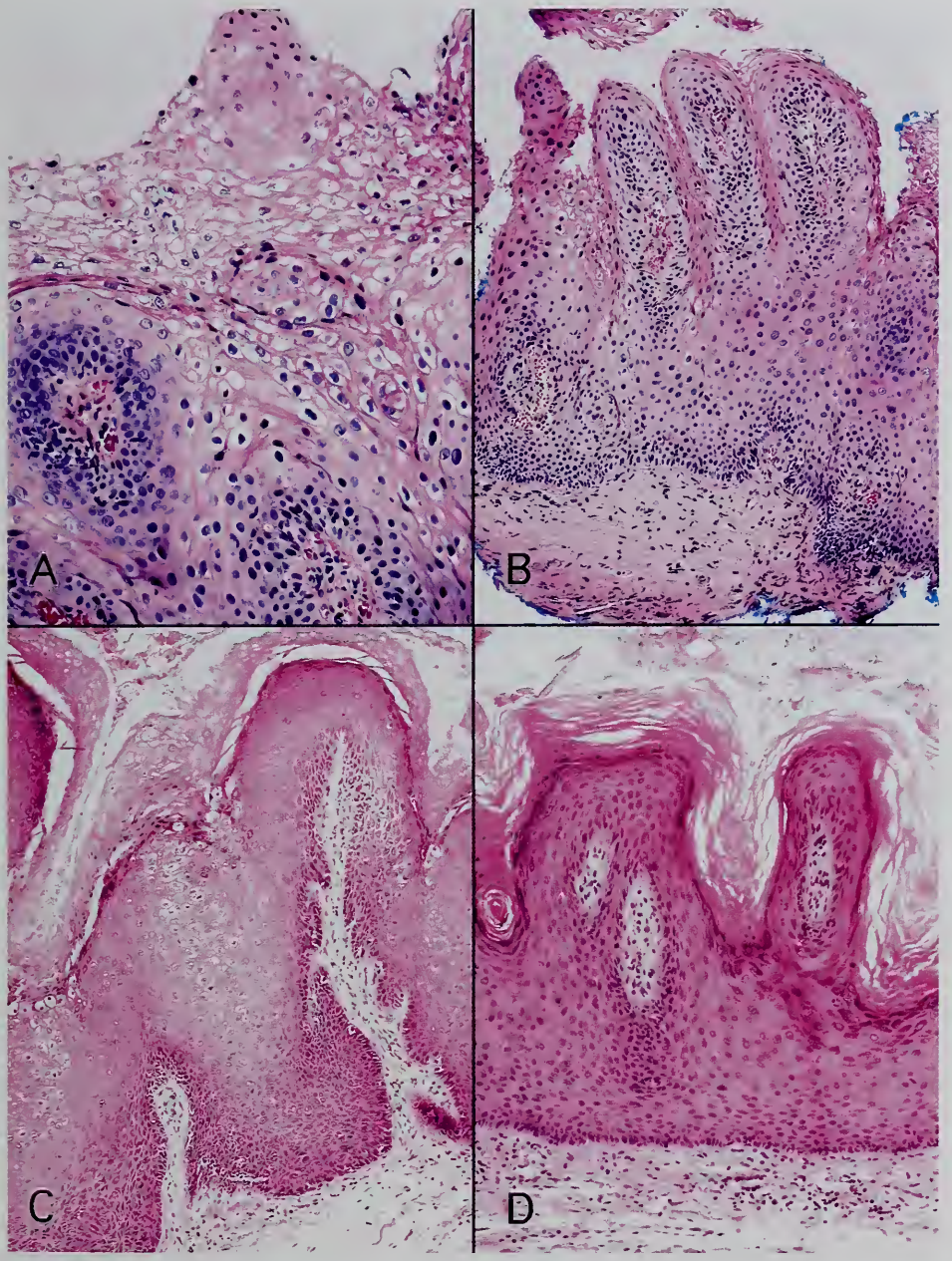


Figure 7-3

CONDYLOMA ACUMINATUM: VERRUCOID GROWTH

All four lesions have prominent parabasal epithelial hyperplasia with marked epithelial proliferation and variable verrucoid growth. A and B are from the vestibular mucosa and do not have a keratin layer, but do have prominent koilocytosis. The lesion in B has delicate vascular papillae and C and D have prominent hyperkeratosis. The lesion in C has associated koilocytosis that is not present in D.

branching papillae are an important architectural feature of condyloma.

The koilocyte is characterized by nuclear enlargement, wrinkling of the nuclear membrane, and cytoplasmic cavitation. Near the surface, in the granular layer, the nucleus of the koilocyte may be shrunken. The nuclear chromatin is hyperchromatic or smudgy. Mitotic figures are characteristically normal but may be increased in number compared with adjacent normal epithelium. Condylomata are typically diploid (392).

The keratinocytes of vulvar flat condyloma acuminatum may lack maturation (fig. 7-3). Apoptosis and degenerative changes are present in the more superficial keratinocytes, a change that has been referred to as pseudobowenoid vulvar change (305). This change resembles podophyllin effect. Approximately 10 percent of condylomata show some nuclear atypia. Lesions classified as condyloma acuminatum that have associated moderate to severe atypia should be classified as *condyloma acuminatum with vulvar intraepithelial neoplasia (VIN), high grade (VIN 2-3).*

Immunohistochemical and Molecular Findings. The capsid protein of HPV is an antigen shared by all papillomaviruses. Approximately 50 percent of typical condylomata,

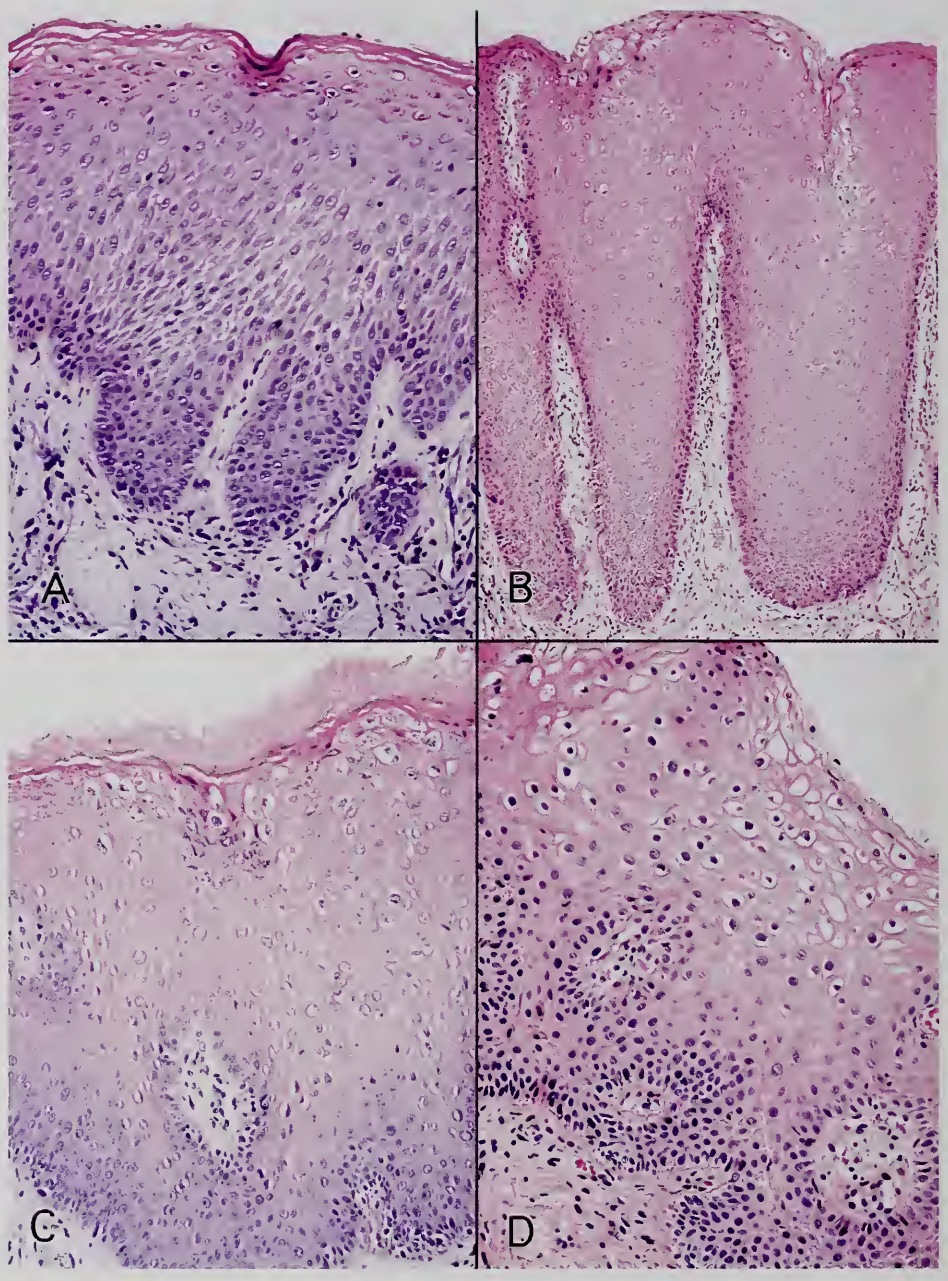


Figure 7-4

CONDYLOMATA ACUMINATA: FLAT GROWTH

All four lesions have prominent parabasal proliferation with variable acanthosis and all four have koilocytosis that is most prominent in C. Lesions in A, B, and C have a keratin layer. The lesion in D is from the mucosa of the vulvar vestibule and lacks a keratin layer.

regardless of their site, are immunoreactive with the commercially available antibody to the capsid antigen. The immunoreactivity is found within the nucleus of the koilocyte, and its presence requires approximately 200 viral copies per nucleus. False negative results in typical vulvar condylomata are related to the presence of insufficient viral antigen, the age of the lesion, prior therapy, or type of tissue fixation. Because of this lack of sensitivity, immunohistochemistry is not useful clinically.

In situ hybridization and PCR are more sensitive and can be of value in confirming the histologic diagnosis of a condyloma (110). Low-risk and high-risk probes are needed because although most vulvar condylomata are HPV type 6/11 positive, some have types 31/33/51 or 16/18 (330). Condylomatous lesions associated with high-risk HPV types, however, usually have nuclear atypia and features sufficient to classify them as VIN. In situ hybridization or PCR, probing for the above HPV types, may be of value because essentially all condylomata contain HPV while lesions that resemble condyloma do not contain HPV (110).

Condylomata have cells in various states of proliferation throughout the epithelium. To

identify these cells in active cell cycle, Ki-67 (MIB-1) is used to distinguish condylomata from fibroepithelial polyps or squamous papillomas. Condylomata that are actively proliferating may express MIB-1 within the upper two thirds of the epithelium, whereas fibroepithelial polyps and papillomas express MIB-1 only in the lower third (330).

Ultrastructural Findings. Electron microscopy has demonstrated HPV particles within the nucleus of the koilocyte in 25 to 50 percent of cases (312,313). The virus is approximately 55 nm in diameter and is occasionally present in the form of filaments. The number of viral particles reaches a peak within 6 to 12 months after inoculation and decreases within 24 to 36 months (312,313).

Differential Diagnosis. The differential diagnosis of a condyloma acuminatum includes fibroepithelial polyp, squamous papilloma, vulvar amyloidosis, and squamous cell carcinoma, particularly the verrucous type (96,209). Fibroepithelial polyps and squamous papillomas do not contain HPV, and do not usually express Ki-67 (MIB-1) in the upper two thirds of the epithelium (330). Vulvar amyloidosis can clinically resemble condyloma or carcinoma. It is readily distinguished by the presence of amyloid in the superficial dermis of the vulvar mass (214,326).

Condylomata may become large, particularly in pregnancy. Large lesions should still be classified as condylomata without the adjective giant to avoid confusion with verrucous carcinoma. Verrucous carcinoma has broad rete ridges and pushing borders and, unlike condyloma acuminatum, may be deeply infiltrative and locally destructive; koilocytosis is absent (see Verrucous Carcinoma).

Another type of squamous cell carcinoma, designated warty (condylomatous) carcinoma, may mimic condyloma acuminatum showing cytologic atypia. This neoplasm, however, is infiltrative, with moderate to marked nuclear pleomorphism. The infiltrating tumor typically has cells with large pleomorphic nuclei and keratinization. Cytoplasmic vacuolization consistent with koilocytosis may be present. In contrast to a condyloma, the base of warty carcinoma has the appearance of invasive squamous cell carcinoma.

Keratoacanthoma has a central keratin plug and an irregular dermal interface. Condyloma acuminatum, especially one that has recently been treated with podophyllin, may have nuclear changes that suggest VIN. VIN, however, has variable degrees of cellular crowding, nuclear pleomorphism, abnormal mitotic figures, and other features that distinguish it from condyloma acuminatum (443).

Treatment and Prognosis. Vulvar condylomata are sexually transmitted. They may regress spontaneously but usually persist or increase in size and number. There is an increased frequency of condyloma in pregnant women, among oral contraceptive users, in women with diabetes mellitus, and in those who are immunosuppressed. Regression of vulvar condyloma may occur after pregnancy (312). Approximately 30 percent of women with vulvar condyloma have associated cervical or vaginal condylomata or intraepithelial neoplasia (312,445). Consequently, before therapy, examination of the entire lower genital tract is necessary to determine the extent of disease. Small lesions are treated by ablation with topical administration of dichloroacetic or trichloroacetic acid, podophyllin-related agents, or topical immunomodulators such as imiquimod. Large lesions are surgically excised using superficial excision, electrosurgical excision or ablation, or laser excision or vaporization.

The association of vulvar condylomata with VIN is recognized and immunosuppressed individuals appear to be at increased risk (59,466). Concurrence of vulvar condyloma acuminatum and squamous cell carcinoma has been observed (96). The giant condyloma of Buschke-Lowenstein is now considered a verrucous carcinoma and reports of this tumor arising within vulvar condyloma may represent examples of malignant transformation. The risk of progression of a typical condyloma to VIN or squamous carcinoma probably depends on the type of HPV it contains and the immunocompetence of the host.

Seborrheic Keratosis

Definition. *Seborrheic keratosis* is a benign epithelial growth characterized by an elevated acanthotic epidermis associated with papillomatosis, hyperkeratosis, and epithelial invaginations forming horn cysts.

General Features. Multiple seborrheic keratoses are common on the hair-bearing skin of the vulva, especially in the elderly. When the superficial portions of lesions are pulled from

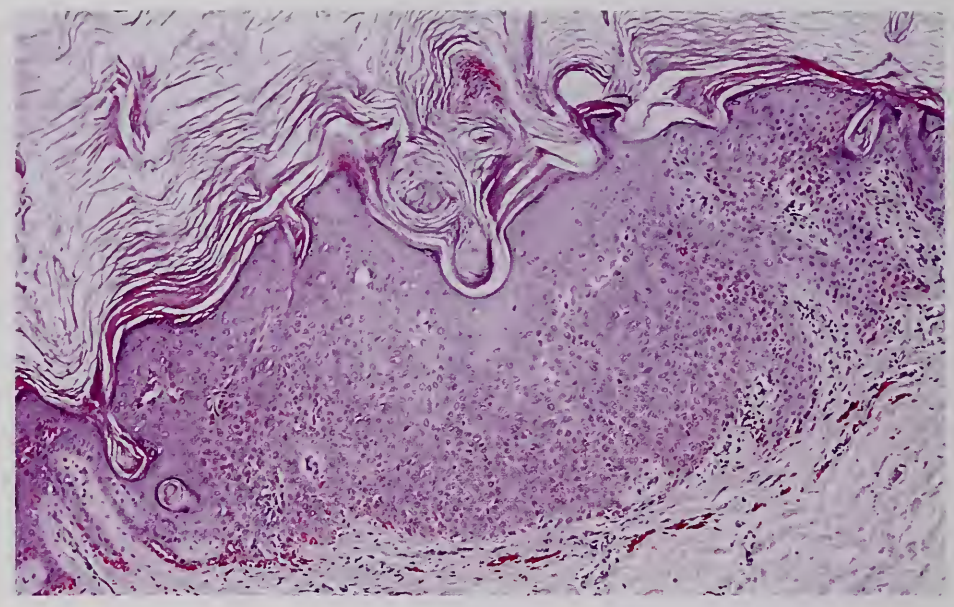


Figure 7-5

SEBORRHEIC KERATOSIS

A nearly straight line can be drawn between the base of the keratosis and the underlying dermis. There is epithelial maturation with a hyperkeratotic surface. Keratin plugs are seen near the surface.

the skin surface, small punctate bleeding sites may be seen beneath them. The *Leser-Trelat syndrome*, characterized by the rapid development of multiple seborrheic keratoses, may herald the appearance of a malignant tumor in an internal organ.

Gross Findings. Seborrheic keratosis is typically a raised, waxy, brown to black lesion. There is a sharp delineation between the lesion and the dermis, creating the appearance that it is tacked on.

Microscopic Findings. On microscopic examination, a nearly straight line can be drawn below the keratosis, with the line intersecting the deep rete ridges of the normal epithelium on both sides of the lesion (fig. 7-5). Hyperkeratosis, papillomatosis, and intraepithelial keratin cysts are characteristic. The squamous cells include basal and parabasal cell types. No significant nuclear atypia is present. Hyperpigmentation, due to the presence of melanin within the basal and lower parabasal cells, is frequently seen.

Differential Diagnosis. Condyloma acuminatum, VIN, basal cell carcinoma, superficial spreading melanoma, squamous cell carcinoma, and other focally hyperplastic epithelial disorders should be considered in the differential diagnosis. Condyloma acuminatum has koilocytosis and dyskeratosis, but keratin cysts are rarely seen. VIN is characterized by nuclear pleomorphism and hyperchromasia and may involve skin appendages. Basal cell carcinoma has smaller cells with dense nuclear chromatin and is typically locally infiltrative in a trabecular or pushing manner. Basal cell carcinoma also commonly expresses BerEP4 (416). Seborrheic keratosis is associated with inverted follicular keratosis that may have a pseudoinfiltrative growth pattern resembling squamous cell carcinoma; significant atypia, mitotic activity, and lack of adjacent VIN or dermal desmoplasia, however, distinguish this lesion from carcinoma (369). Malignant melanoma has nuclear pleomorphism and contains melanoma antigen (HMB45, Melan-A) and S-100 protein antigen. Lichen simplex chronicus does not contain keratin pearls or exhibit papillomatosis.

Treatment and Prognosis. A decision to treat is based on the judgement of the clinician and the needs of the patient. A superficial or shave biopsy is recommended for diagnosis. Therapy in nonpregnant patients includes superficial excision, electrosurgical or laser excision, fulguration, topical podophyllin or podophyllin-related agents, topical trichloroacetic acid, cryotherapy, topical immunomodulator (imiquimod) therapy, and other methods.

Epidermolytic Acanthoma

Epidermolytic acanthoma is a rare benign vulvar neoplasm that presents as multiple, verrucoid, slightly pigmented, circumscribed nodules usually 5 mm or less in diameter. In one case several lesions were present on the medial aspect of the labia majora (88). There are prominent acanthosis and hyperkeratosis, a prominent granular layer, and granular degeneration of all

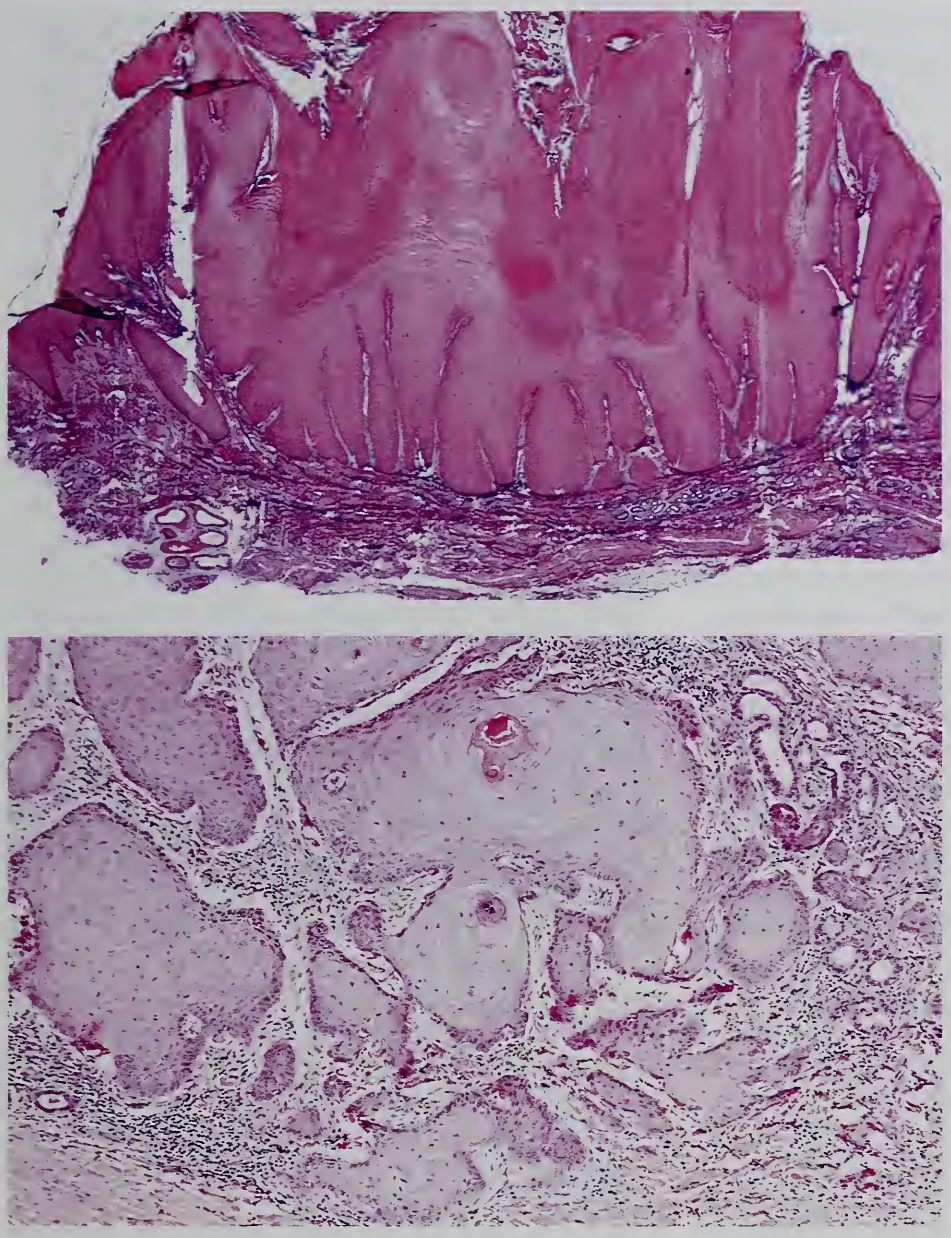


Figure 7-6

KERATOACANTHOMA

Top: Although the deeper portions of this keratoacanthoma appear somewhat irregular and infiltrative, the tumor dermal interface is well defined, with the epithelium compressing the dermal papillae with marked acanthosis. A surface keratotic plug is present.

Bottom: Tongues of epithelium extend into the dermis and some keratinization is present. The tumor cells are well differentiated. The dermis at the tumor-dermal interface has a mild chronic inflammatory infiltrate.

but the basal and parabasal layers. Within the granular layer are numerous irregularly shaped keratohyaline bodies.

Keratoacanthoma

Keratoacanthoma is a benign neoplasm arising from follicular infundibular epithelium. It is composed of well-differentiated squamous epithelium and has a central keratin-filled crater and an infiltrative border. The tumor typically regresses spontaneously within 6 months, although most are excised rather than observed. Keratoacanthomas are rare on the vulva (65,356).

Keratoacanthomas are rapidly growing solitary tumors with hard, raised, rough, irregular, nonulcerated surfaces. They rarely exceed 2.5 cm in diameter and are usually not tender or inflamed. A central keratinous plug may protrude in a horn-like manner from the surface.

On microscopic examination, the base of the lesion is a symmetrical, cup-like mass filled with keratin and surrounded by bland-appearing squamous cells with prominent eosinophilic cytoplasm. In early lesions, the squamous cells may have nuclear atypia and mitotic activity. The squamous cells have a "pushing" margin, although focal clusters of neoplastic squamous cells may be seen immediately adjacent to the tumor (fig. 7-6). The surface epithelium adjacent to the lesion, unlike in squamous carcinoma, is

usually unremarkable. A dense, mixed inflammatory cell infiltrate is usually present in the adjacent dermis, and a foreign body reaction may also be evident.

Keratoacanthoma may be difficult to distinguish from squamous cell carcinoma, and there is debate as to whether keratoacanthoma should be considered a very low-grade indolent squamous carcinoma. Squamous cell carcinoma, however, typically lacks a keratin crater and has a more irregular infiltrating margin. Treatment of keratoacanthoma is usually excisional biopsy.

Folliculosebaceous Cystic Hamartoma

Folliculosebaceous cystic hamartoma is a benign neoplasm resembling a disorganized pilosebaceous unit. It is rare on the vulva, where, as in other sites, it presents as an asymptomatic papule or nodule. Histologically, it is a cystic mass, lined with squamous epithelium and encompassed by disorganized hyperplastic sebaceous lobules and fibrous tissue (31). The sebaceous differentiation is significantly greater than that seen with trichofolliculoma.

Nevus comedonicus is also a hamartomatous neoplasm of the pilosebaceous unit that may occur in the vulva. One case was reported in a 6-year-old (143).

Trichofolliculoma

Trichofolliculoma is a benign skin adnexal neoplasm associated with hair follicles (327). It is typically a small, solitary dermal mass less than 0.5 cm in diameter. The tumor is located in the superficial dermis and is lobular in character, forming a cystic mass lined with basaloid type cells that have a variable degree of sebaceous differentiation. Fine hairs are usually seen with the keratinous material that fills the cyst. The lumen of the cystic mass may communicate with the epithelial surface as an epithelial invagination, resembling a vulvar vestibular cleft or epithelial infolding. Trichofolliculomas associated with VIN have been reported (327).

Vulvar Intraepithelial Neoplasia (Vulvar Squamous Intraepithelial Neoplasia)

Definition. *Vulvar intraepithelial neoplasia* (VIN) is a proliferative intraepithelial squamous lesion displaying abnormal maturation, nuclear enlargement, and atypia. Pleomorphism, coarse chromatin clumping, and irregular nuclear contours characterize the epithelial nuclear atypia. These lesions are designated as high-grade VIN (VIN 2 or VIN 3) or low-grade VIN (VIN 1). They have also been designated as VIN grades 1, 2, and 3, and as *dysplasia* (mild, moderate, severe) and *carcinoma in situ* (293,359,465).

General Features. Unlike vulvar carcinoma, the incidence of VIN has increased over the past 20 years, especially in women of reproductive age (74). Patients have vulvar pruritus (the most common symptom) or irritation, or observe the lesion and seek medical assistance (468). One third of the patients are asymptomatic. The most common sites of VIN are on the labia minora and the perineum. Perianal involvement occurs in approximately one third of patients and may extend into the anus. Approximately 70 percent of VIN lesions are multifocal (50,52, 83,126,146,194,322,335,465,472).

The clinical appearance is variable. Over 50 percent of the lesions are white or aceto-white with the application of 3 percent acetic acid, with the remainder brown, black, or red. They may be plaque-like, but are often macular or papular (fig. 7-7).

Microscopic Grading and Subtyping. In this Fascicle, flat lesions with koilocytosis, minimal evidence of proliferation, and atypia limited to the lower third of the epithelium are classified as VIN 1 or low-grade VIN (fig. 7-8). The term atypical condyloma acuminatum, or flat condyloma acuminatum, is not recommended. In cases of condyloma acuminatum with VIN, the VIN is high grade, encompassing VIN 2 and VIN 3. For such lesions, the authors recommend the term high-grade VIN (VIN 2-3) with condyloma acuminatum. The International Society for the Study of Vulvovaginal Disease has recommended that the term VIN be used alone, not graded, and used to describe high-grade VIN lesions only (VIN 2 or VIN 3). It also recommended that the term low-grade VIN (VIN 1, or mild dysplasia), not be used and that such lesions be classified as flat condyloma acuminatum, or given an appropriate descriptive term (393). Issues regarding the recommendation to not use the term VIN 1 are challenged by recent evidence that low-grade VIN lesions are associated with high-risk HPV in approximately 40 percent of cases studied; prospective studies

Figure 7-7

VULVAR
INTRAEPITHELIAL NEOPLASIA

There are numerous macular and papular lesions that involve the labia majora, perineum, and perianal skin. The lesions are predominately pigmented. (Courtesy of E.G. Friedrich Jr., Gainesville, FL.)

on the clinical behavior of such cases remain to be performed (405).

VIN lesions are graded in the most severely involved areas. In low-grade VIN (VIN 1) lesions, the cellular proliferative changes are present in the lower third of the epithelium, with maturation of the surface epithelium. Koilocytosis may be present (fig. 7-8).

The cellular changes and atypia of high-grade VIN (VIN 2-3) lesions typically involve the middle or upper third of the epithelium (fig. 7-9). Abnormal mitotic figures are generally easily found. Surface maturation may include a granular layer and a variable degree of hyperkeratosis.

High-grade VIN lesions demonstrate considerable morphologic heterogeneity. Studies suggest that the different morphologic patterns may reflect differing etiologies (319,423). VIN is subdivided into three types: warty (condylomatous), basaloid (usual), and differentiated (simplex) types related to the cellular characteristics of the lesion. Unfortunately, interobserver reproducibility for subtyping these three VIN lesions is only fair (kappa 0.31-0.42) (424). Some lesions have mixed basaloid and warty patterns. A rare pagetoid type of VIN is also recognized (344). Some VIN lesions are mixed or not readily classifiable into one of these groups.

Warty VIN is characterized by marked proliferation, parakeratosis, hyperkeratosis, and focal koilocytosis (figs. 7-9, 7-10A, 7-11). The epithelium typically displays an undulating or spiked surface, creating a warty or condylomatous appearance. Although there is marked proliferation, as evidenced by acanthosis and numerous mitotic figures, including abnormal mitotic figures, the cells show evidence of maturation, albeit abnormal. Individual cells have well-defined cell membranes with prominent eosinophilic cytoplasm. Individual cell keratinization is often observed. The nuclei are enlarged, with coarsely granular chromatin, and there is an increased nuclear-cytoplasmic ratio. Cells with hyperchromatic, shrunken nuclei surrounded by clear cytoplasm are characteristic. Koilocytotic atypia involving the surface epithelium may be present. Multinucleated epithelial giant cells are often observed. Rete pegs are typically wide, extend deeply into the stroma, and are separated by thin stromal papillae that often penetrate close to the surface.

Basaloid VIN is characterized by thickened epithelium with a smooth, relatively flat surface that lacks the undulated and spiked appearance of warty VIN. Hyperkeratosis is variably present, but not to the extent observed in warty VIN. The epithelium is either entirely or almost entirely composed of atypical immature parabasal type cells, similar to the classic appearance of carcinoma in situ of the cervix (CIN 3) (figs. 7-10B,C, 7-12. Individual cells have poorly defined cell membranes, scant cytoplasm, and enlarged hyperchromatic nuclei. Koilocytosis involving the surface occurs, but less frequently than in warty VIN. Mitotic figures, including abnormal mitotic figures, are numerous. As with warty VIN, the intraepithelial process frequently extends into

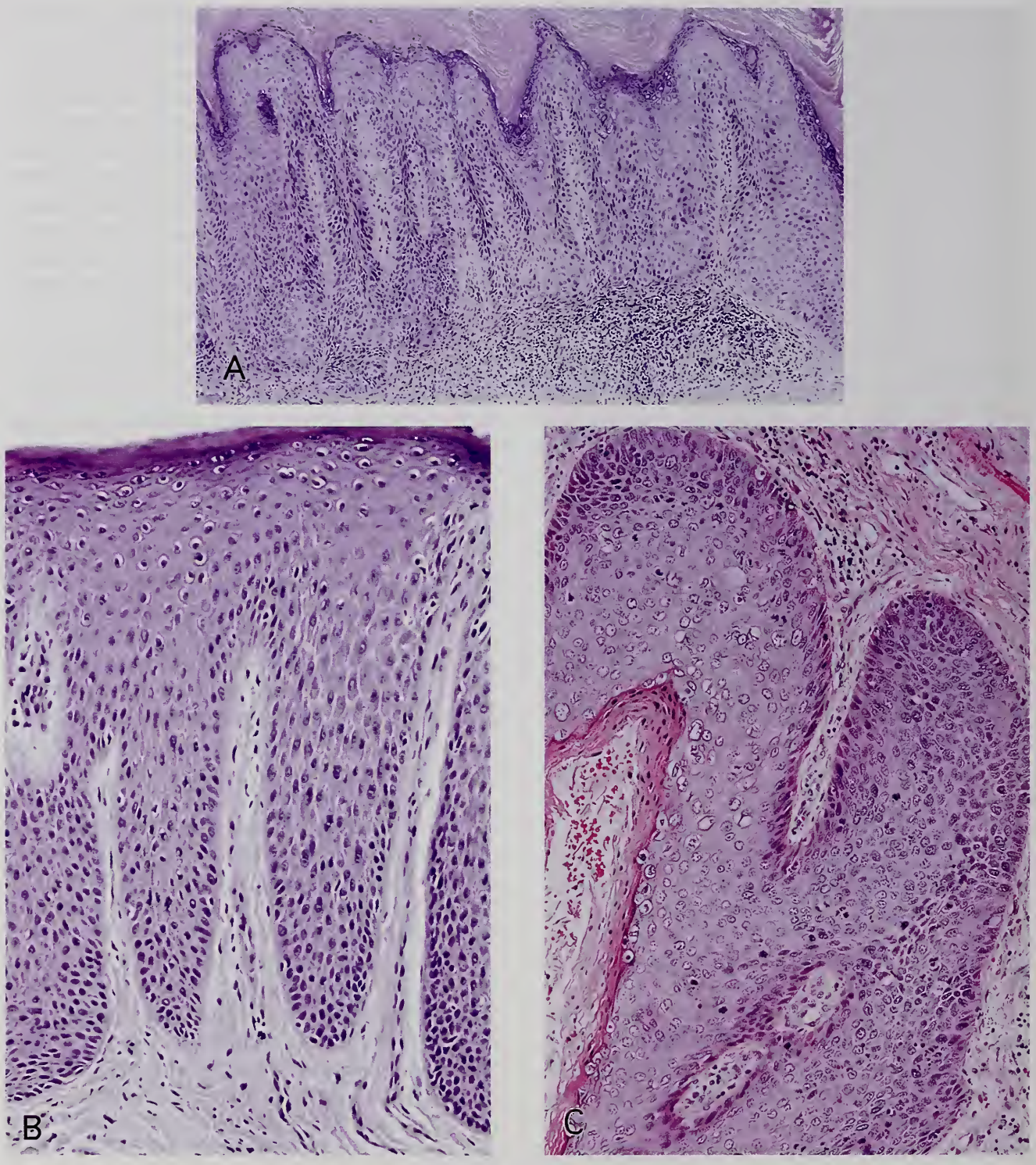


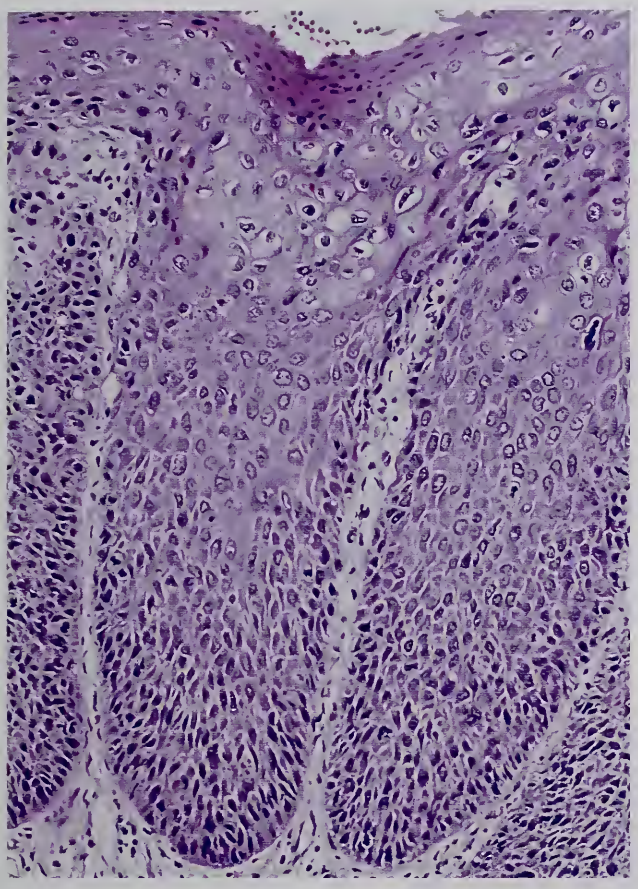
Figure 7-8

VULVAR INTRAEPITHELIAL NEOPLASIA, LOW-GRADE (VIN 1, MILD DYSPLASIA)

A: This lesion has a micropapillary, or spiked, surface pattern with marked acanthosis, hypergranulosis, and hyperkeratosis. Koilocytosis is not apparent. The lower third of the epithelium lacks maturation and nuclear pleomorphism. Some chronic inflammation is present in the superficial dermis.

B: This lesion has features of condyloma acuminatum, with a verrucoid pattern of growth. Some koilocytosis is present near the surface. The lower third of the epithelium lacks maturation.

C: There is prominent acanthosis, with lack of maturation, in the lower epithelium. Some koilocytosis is present in the upper third.



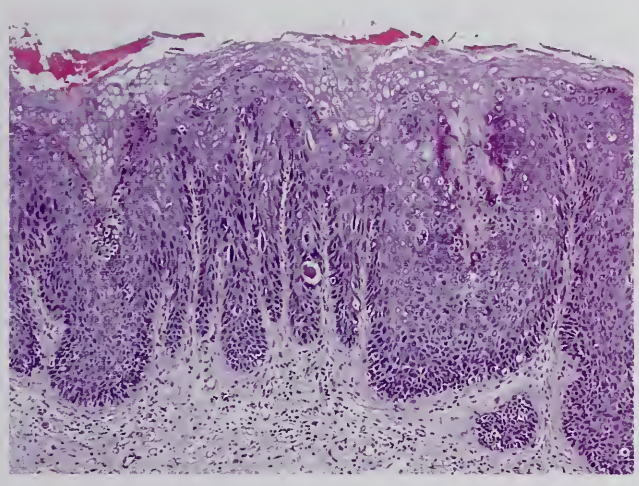


Figure 7-9

VULVAR INTRAEPITHELIAL NEOPLASIA, HIGH-GRADE (VIN 2, MODERATE DYSPLASIA)

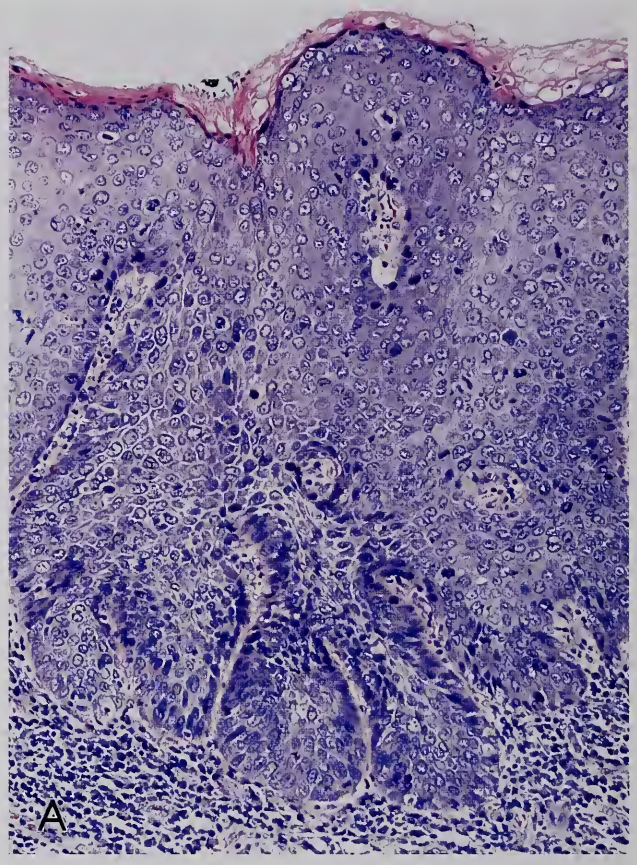
Left: Prominent acanthosis is present in this warty type lesion. The keratinocytes within the lower half of the epithelium lack maturation and have nuclear atypia with some mitotic figures. Koilocytosis is present in the more superficial epithelium.

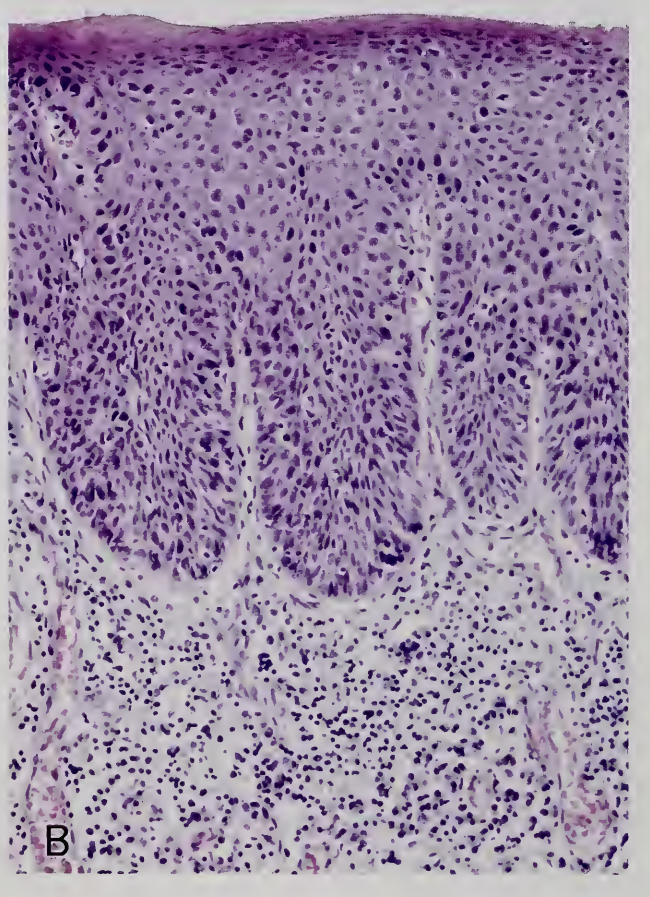
Above: This lesion has mitotic figures and moderate nuclear pleomorphism and lacks maturation in the lower half of the epithelium. Koilocytosis is present in the superficial epithelium.

hair follicles and adnexal structures. Basaloid and warty VIN may be present adjacent to invasive squamous cell carcinoma of the basaloid or warty type, respectively, although basaloid VIN also occurs adjacent to warty carcinoma and warty VIN adjacent to basaloid carcinoma (see Invasive Squamous Cell Carcinoma).

The *differentiated (simplex) type of VIN* is classified as *VIN 3, differentiated (simplex type),* and is characterized by abnormal cells confined to the basal and parabasal portions of the rete pegs (figs. 7-13, 7-14) (2,166). The superficial layers show normal maturation, although mild to moderate nuclear atypia may be present. In the basal areas, the epithelial cells may have prominent eosinophilic cytoplasm, and keratin pearl formation may be present. The nuclei have dispersed chromatin and typically prominent nucleoli. This type of VIN is often found adjacent to the typical type of keratinizing squamous cell carcinoma and is associated with lichen sclerosus in older women (229,456,476). In one study, 10 of 12 patients with differentiated VIN had squamous cell hyperplasia adjacent to the tumor, and 4 of 12 had associated lichen sclerosus (476). Only 1 of the 12 patients had evidence of HPV, however, p53 was expressed in the suprabasal cells in 10 of the 12 patients (fig. 7-13C). Differentiated VIN is distinguished from other types of VIN by the presence of cells with prominent increased eosinophilic cytoplasm and nuclear chromatin changes, including radial dispersion of chromatin and prominent nucleoli (166). In addition, keratin pearl formation is seen commonly in differentiated VIN but is rare in other VIN lesions.

Pagetoid VIN is rare and only a few cases have been reported (344). The lesion is characterized by the formation of clusters and nests of neoplastic intraepithelial cells. The clusters of atypical cells are within otherwise normal epithelium. These cells may have pale cytoplasm and nuclei with relatively clear chromatin and prominent nucleoli resembling cutaneous Paget cells. Although these cells are immunoreactive for cytokeratin (CK) 7, they are not immunoreactive for CK20, carcinoembryonic antigen (CEA), S-100 protein, or Melan-A, and otherwise have features of VIN, not Paget disease or melanoma (106).





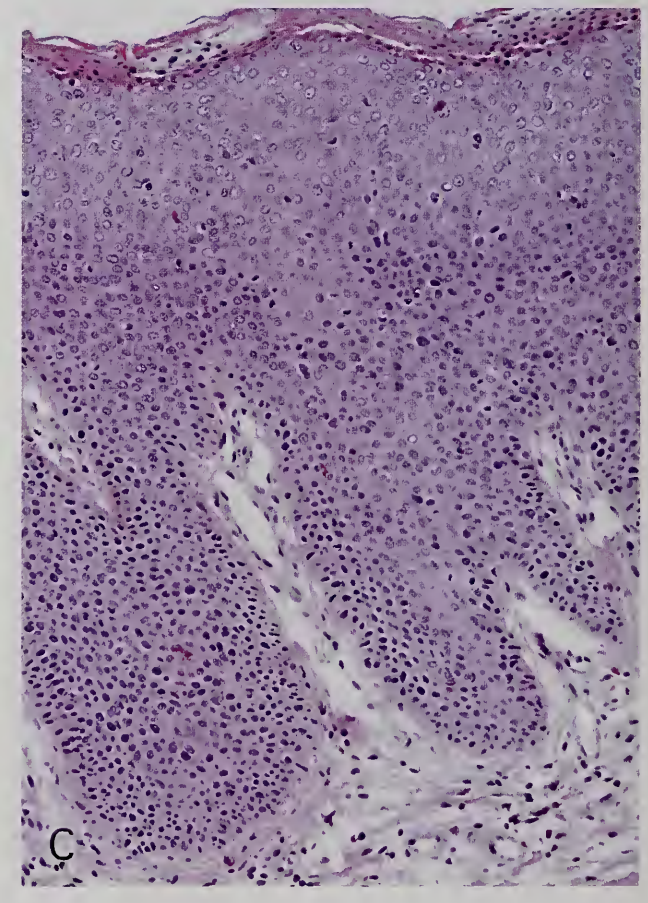


Figure 7-10

VULVAR INTRAEPITHELIAL NEOPLASIA, HIGH-GRADE (VIN 3, SEVERE DYSPLASIA)

A: There is prominent acanthosis with hyperkeratosis in this warty type lesion. Cellular maturation is lacking in the lower two thirds of the epithelium. Nuclear pleomorphism and hyperchromasia are present. The hyperkeratosis does not influence grading.

B: The maturation in this basaloid type is limited; abnormal cellular maturation is manifested by keratinocytes with nuclear hyperchromasia and pleomorphism. The lack of maturation in the small cells mimics that of basal cells.

C: Epithelial maturation is lacking in this basaloid type. There is no parakeratosis or hyperkeratosis. Nuclear pleomorphism and hyperchromasia are present. A moderate superficial chronic inflammatory infiltrate is seen within the dermis.

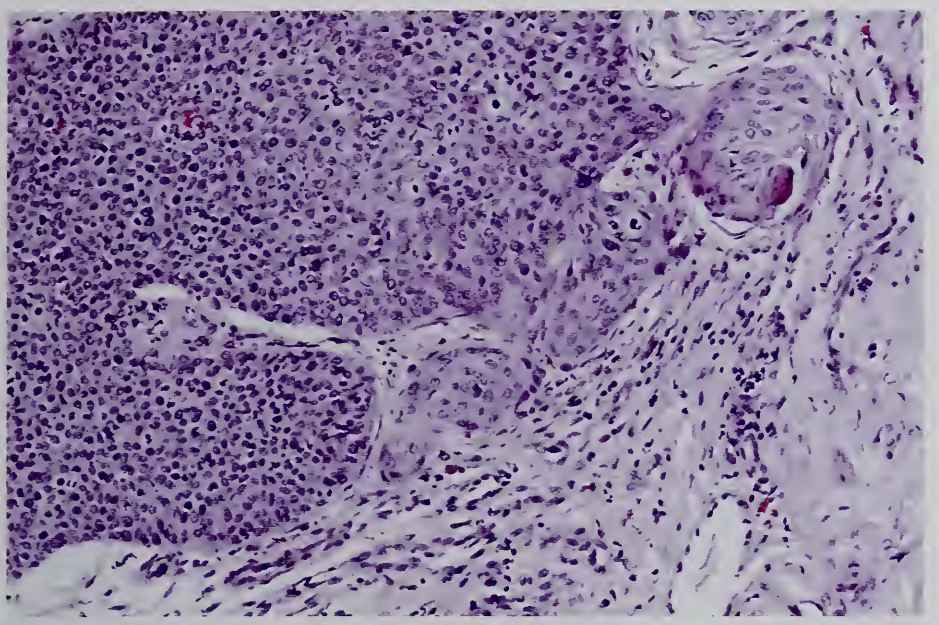


Figure 7-11

VULVAR INTRAEPITHELIAL NEOPLASIA, HIGH-GRADE (VIN 3)

Little cellular maturation is present in this warty type lesion with parakeratosis, hyperkeratosis, and adjacent hypergranulosis.

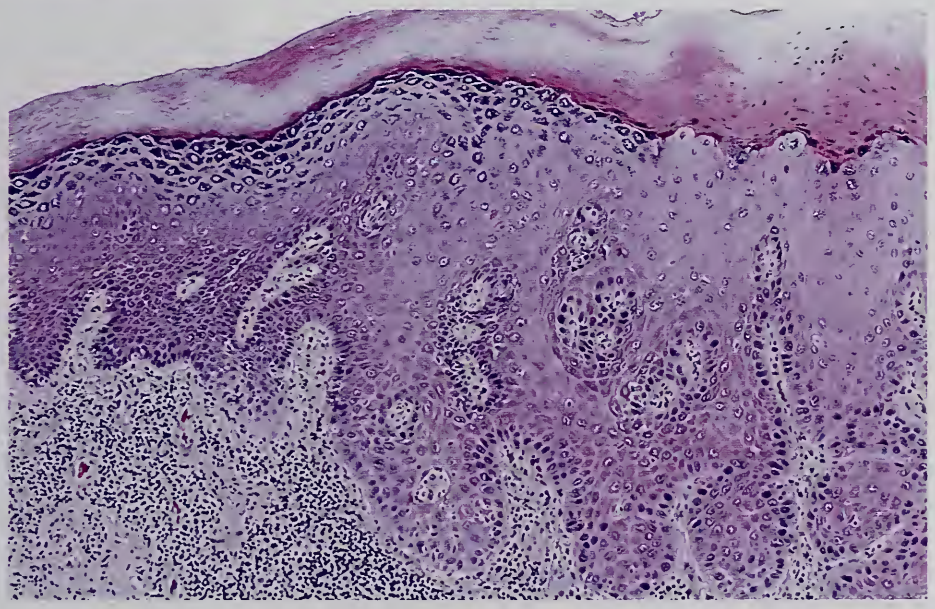


Figure 7-12

VULVAR INTRAEPITHELIAL NEOPLASIA (VIN 3)

The epithelium in this basaloid type lesion, with superficially invasive squamous cell carcinoma, has complete loss of maturation. At the base of one rete ridge is a focus of invasive squamous cell carcinoma, characterized by loss of the orderly palisade orientation of the basal keratinocytes. The invasive focus has cells with increased cytoplasm compared to the basaloid cells of the VIN lesion.

Although each of these types of VIN 3 exists in a pure form, mixtures of warty and basaloid VIN are common. In these instances, the lesion is classified according to the predominant type. Distinguishing warty from basaloid VIN has not been shown to have clinical significance. The differentiated type of VIN is rarely associated with the other types. Unless otherwise specified, the term VIN without further specification in this Fascicle includes both the warty and basaloid forms.

Immunohistochemical Findings. The cells of VIN are immunoreactive for some low and high molecular weight keratins (106). Evidence of alterations in the p16/pRb/cyclin D1 pathway have been demonstrated in VIN lesions, with approximately two thirds of lesions showing epigenetic silencing of p16INK4a. The basaloid and warty VIN lesions typically express p16INK4a (fig. 7-15) (378). In one study, p16INK4a was immunoreactive in 92 percent of high-grade VIN lesions, and in these cases, nearly the full thickness of the epithelium was immunoreactive (372). In contrast, only 2 of 10 low-grade VIN lesions were immunoreactive, and the reactivity was limited to the neoplastic-appearing cells predominately in the lower half of the epithelium.

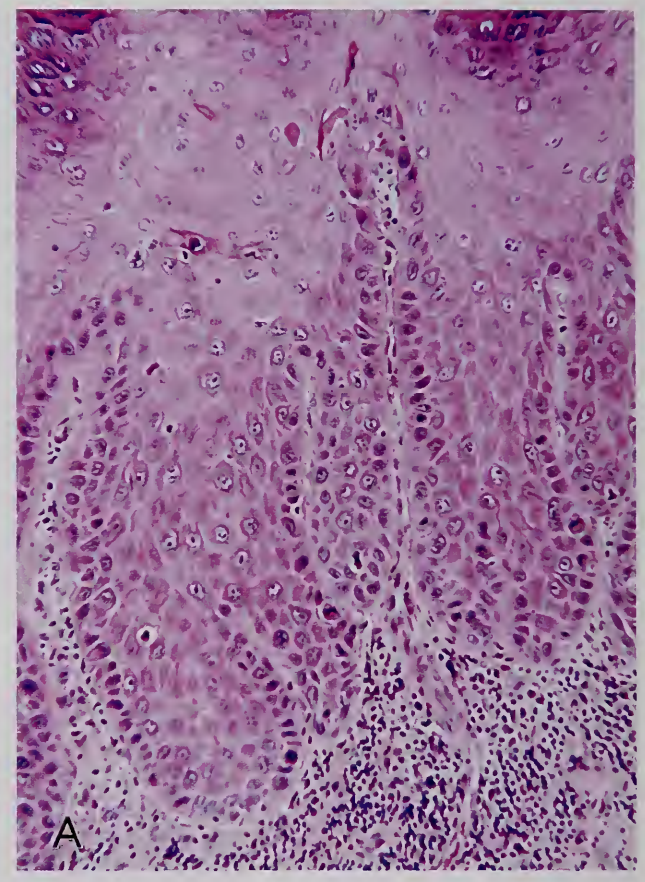
Figure 7-13

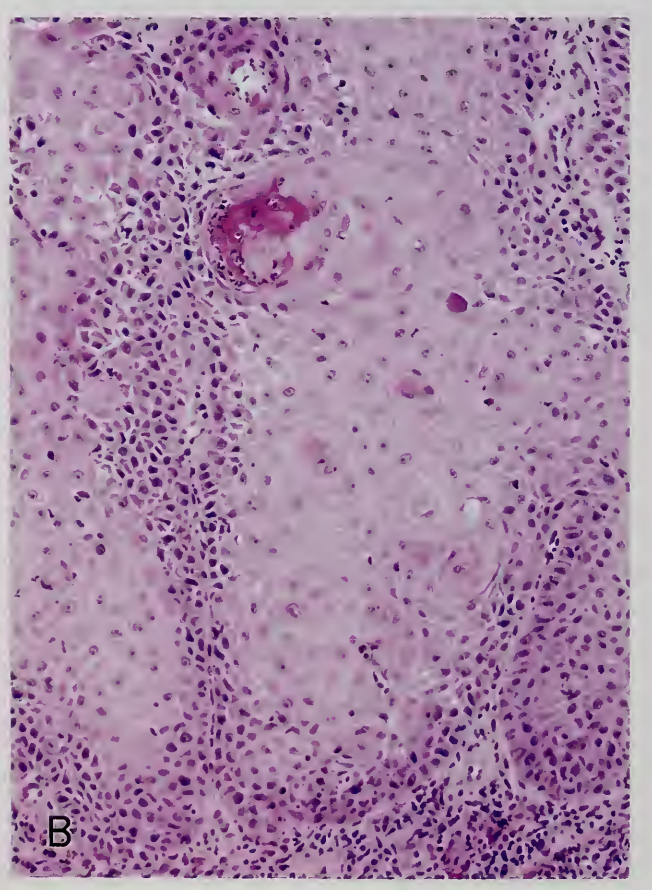
VULVAR INTRAEPITHELIAL NEOPLASIA (VIN 3), DIFFERENTIATED TYPE

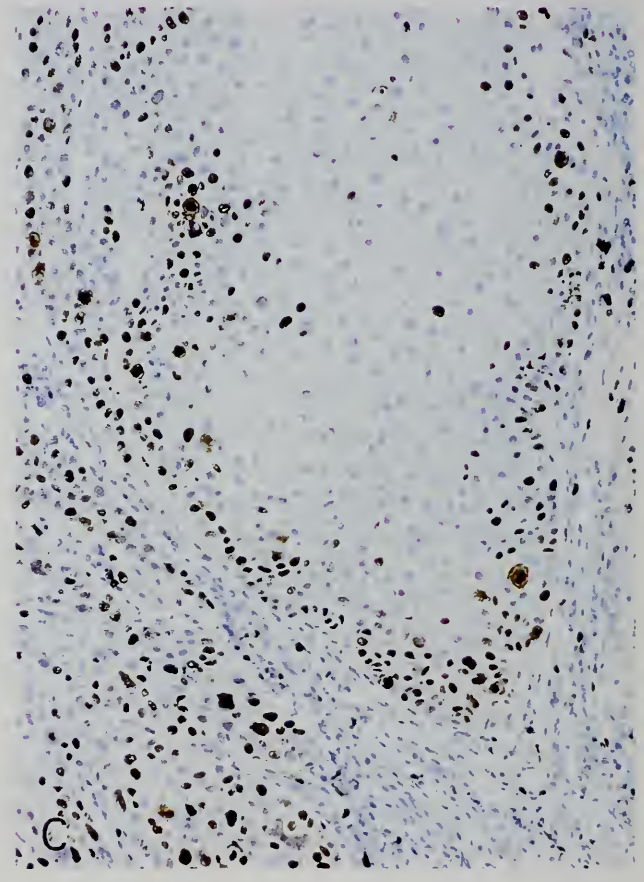
A: There is some loss of epithelial maturation. The keratinocytes have prominent eosinophilic cytoplasm present focally in basal and parabasalar cells. The keratinocyte nuclei have chromatin clearing with prominent nucleoli.

B: Abnormal keratinocytes, with increased eosinophilic cytoplasm and nuclei with prominent nucleoli, are present throughout the epithelium. These cells lack the nuclear hyperchromasia characteristic of other VIN lesions.

C: An immunohistochemical stain for p53 demonstrates nuclear immunoreactivity in the basal and suprabasal cells.







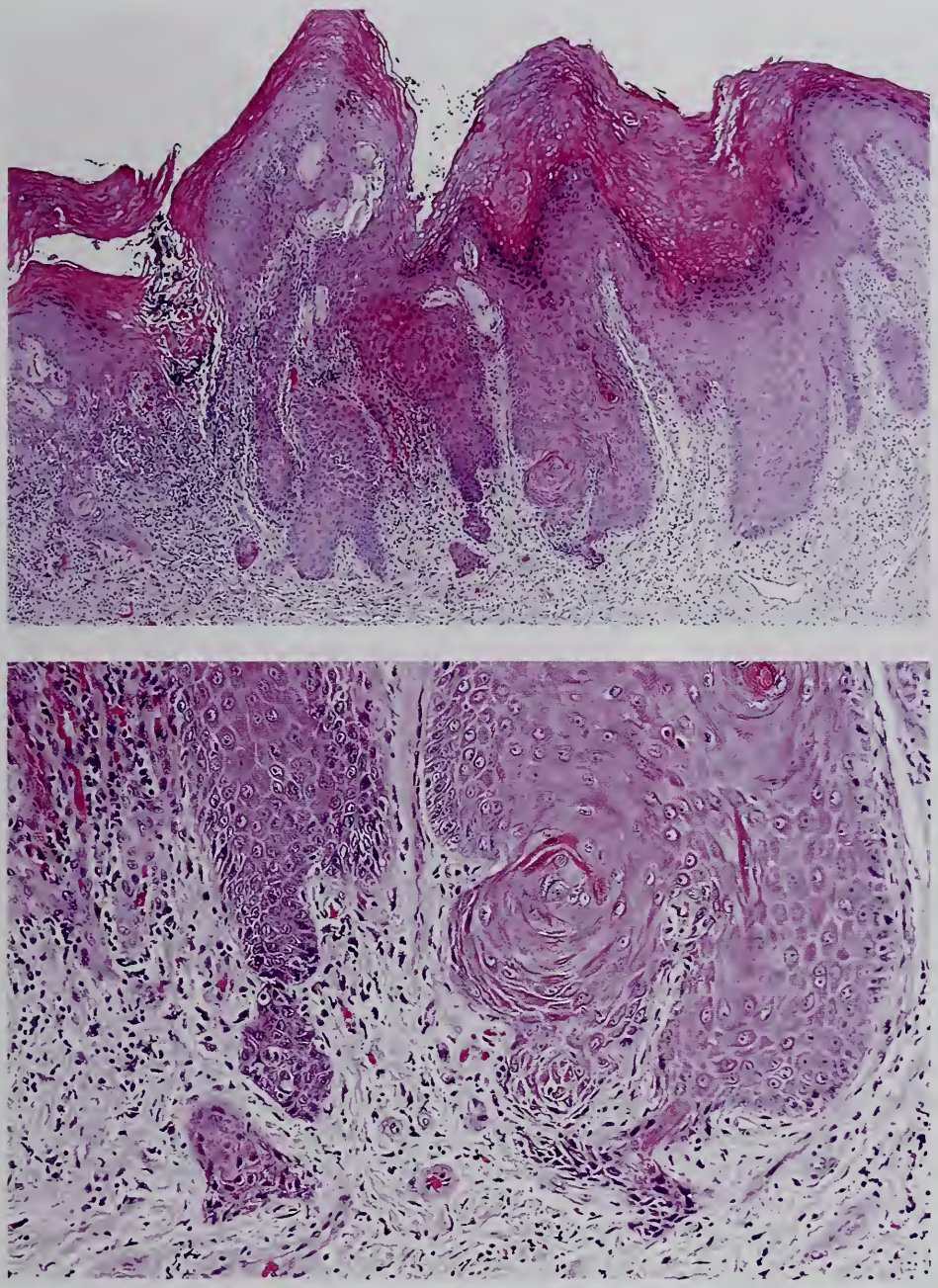


Figure 7-14

VULVAR INTRAEPITHELIAL NEOPLASIA (VIN 3), DIFFERENTIATED TYPE WITH SQUAMOUS CELL CARCINOMA

Top: Abnormal keratinocytes, with increased eosinophilic cytoplasm and nuclei with prominent nucleoli, are present throughout the epithelium. There is hyperkeratosis and prominent acanthosis.

Bottom: Invasive squamous cell carcinoma is present in the dermis, contiguous with the overlying differentiated VIN.

VIN lesions are not immunoreactive for CEA, S-100 protein, or melanoma antigen. HPV is usually present; type 16 is the most common type present in VIN lesions of the warty and basaloid types, and significantly less common in VIN of differentiated type (83,229,319,373,378). Approximately a third of 13 cases of VIN showed overexpression of cyclin D1 (232). None of these cases demonstrated lack of pRb protein. In differentiated VIN, p53 is usually expressed in the basal and some parabasal cells (476). Immunohistochemical studies for cellular proliferation employing bcl-2 and Ki-67 (MIB-1) do not appear to be of much value in the diagnosis of VIN lesions (437).

Differential Diagnosis. Some investigators have recommended distinguishing a multifocal, pigmented, papular lesion with features of VIN, designated bowenoid papulosis, from VIN (444). Studies have shown, however, that microscopically, bowenoid papulosis and VIN are indistinguishable (29,460). Furthermore, these multifocal papular lesions, like VIN 3, contain HPV 16 (29,83,149). Accordingly, the term bowenoid papulosis is not acceptable as a histopathologic diagnosis although it may have

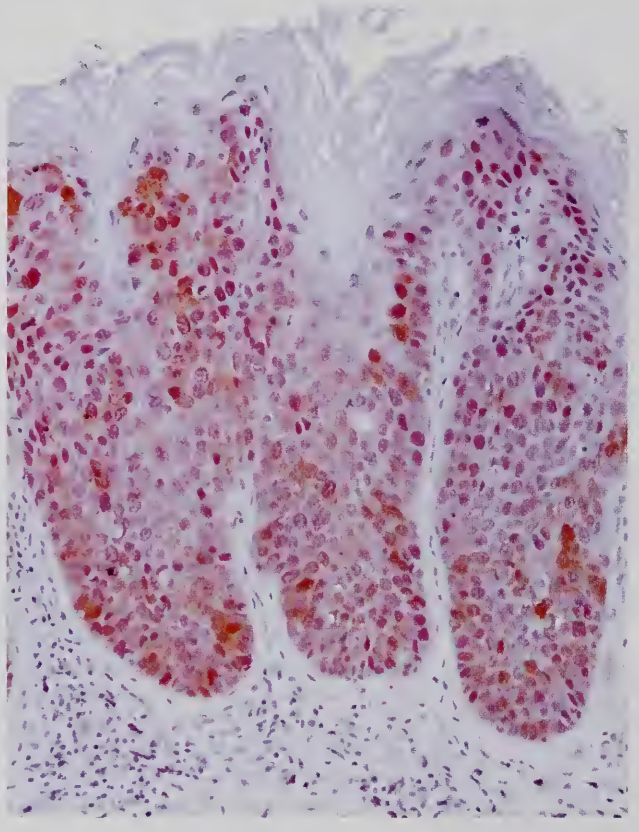


Figure 7-15

p16INK4 EXPRESSION IN VIN 3, WARTY TYPE

Reactivity is present in the keratinocyte nuclei and cytoplasm, and throughout the epithelium in this high-grade VIN.

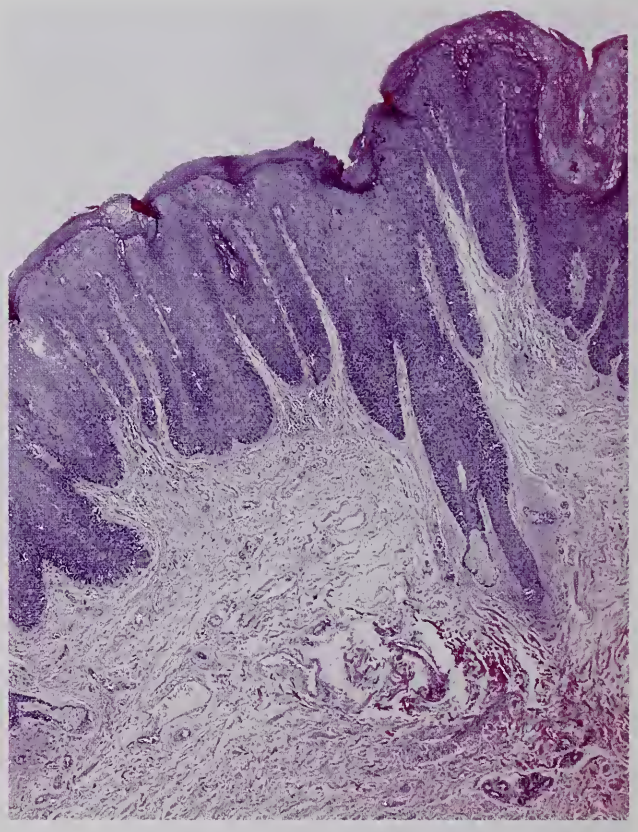


Figure 7-16

VIN 3, WARTY TYPE INVOLVING A SKIN APPENDAGE

The palisaded orientation of the basal keratinocytes is maintained, and contiguous sebaceous gland elements are present.

value clinically to describe the somewhat distinctive pigmented papules (359,465). Cases filling the criteria of bowenoid papulosis have been observed to regress without treatment (191,193,194).

The differential diagnosis of VIN includes invasive squamous cell carcinoma, Paget disease, pagetoid urothelial intraepithelial neoplasia (PUIN), superficial spreading melanoma, basal cell carcinoma, seborrheic keratosis and condyloma acuminatum, including condyloma acuminatum with podophyllin effect, and multinucleated atypia of the vulva (74,265,461).

Skin appendage involvement by VIN is distinguished from invasive squamous cell carcinoma by the preservation of a distinct epithelial dermal junction, lack of dermal desmoplasia, lack of an inflammatory response, evidence of skin appendage epithelial elements deep or adjacent to the area in question, and absence of isolated small clusters of neoplastic squamous cells in the adjacent dermis (fig. 7-16) (389). The radial growth of VIN may result in replacement of the epithelium of the skin appendages by VIN. Skin appendage involvement occurs in approximately 20 percent of the cases in which the lesion is confined to a nonhair-bearing area, and 30 percent of the cases in which the hair-bearing skin is involved. Skin appendage involvement by VIN may be 2.7 mm or deeper in hair-bearing areas (389). The skin appendages and minor vestibular glands are more superficial in nonhair-bearing areas. Epithelium involved by VIN may range from 0.10 to 1.90 mm, with a mean of 0.52 mm. (26). In vulvar nonhair-bearing epithelium, VIN involvement of the sebaceous or vestibular gland epithelium rarely exceeds 1.0 mm in depth below the basement membrane of the overlying surface epithelium. In hair-bearing skin, VIN involvement of the hair follicles rarely exceeds 2.5 mm, being confined within the basement membrane of the hair follicle epithelium (389). Nests of malignant cells beyond

these depths are highly suggestive of invasion. The presence or absence of invasion requires meticulous evaluation of the entire specimen. High-grade VIN may be associated with trichofolliculoma, a benign skin adnexal neoplasm associated with hair follicles (327).

The presence of more than three intraepithelial eosinophils per high-power field, or five or more intraepithelial eosinophils per 10 high-power fields, in a VIN 3 lesion has been reported to be associated with adjacent vulvar squamous cell carcinoma. Increased intraepithelial eosinophils in a biopsy demonstrating VIN 3 may reflect an associated invasive squamous carcinoma; however, this observation requires further study (404).

In contrast to VIN, Paget disease of cutaneous and noncutaneous types has distinctive large atypical cells with large nuclei and cytoplasm that is distinctive from the cytoplasm of the adjacent keratinocytes. The Paget cells occur in clusters, and as single cells within otherwise normal-appearing squamous epithelium.

Immunoperoxidase methods assist in distinguishing VIN, melanoma, Paget disease, and PUIN. Paget disease of cutaneous or anorectal origin typically is immunoreactive for CEA and almost always contains stainable mucin. PUIN usually expresses uroplakin III. VIN lesions typically do not express either CEA or uroplakin III (43,461).

Superficial spreading malignant melanoma has large atypical cells within the epithelium that are immunoreactive for S-100 protein and melanoma antigen (HMB45) or Melan-A. Unlike VIN, melanoma does not express keratin. Some VIN lesions contain melanin within the neoplastic cells.

Basal cell carcinoma characteristically has smaller cells than VIN, and the invasive nests show peripheral palisading of nuclei. A desmoplastic or fibrotic reaction usually surrounds the invasive nests of basal cell carcinoma, and they express BerEP4 (416).

Seborrheic keratosis is composed of a uniform population of cells with prominent hyperkeratosis and intraepithelial keratin pearl formation. Significant nuclear pleomorphism, hyperchromasia, and abnormal mitotic figures are absent in this lesion.

Condyloma acuminatum typically grows in an exophytic, papillomatous, or verrucous pattern and lacks marked nuclear pleomorphism, hyperchromasia, or abnormal mitotic figures. VIN and condyloma may coexist, however: VIN may be present within, or adjacent to, condyloma acuminatum and in such cases both terms should be included in the diagnosis.

Topical podophyllin results in mitotic arrest. With mitoses arrested in metaphase, abnormal mitoses may be seen. Nuclear disruption, dispersion of nuclear chromatin, and cellular swelling are common with podophyllin effect but rarely found with VIN. Nuclear pleomorphism is typically present in VIN; with podophyllin effect, however, the nuclei remain relatively uniform. Unlike VIN, the cellular changes associated with podophyllin effect regress within 2 weeks of discontinuing the applications, and therefore podophyllin should not be used for at least 2 weeks before biopsy.

Multinucleated atypia of the vulva has multinucleated keratinocytes within the lower to middle epithelial layers, without significant nuclear atypia (74).

Differentiated VIN may be difficult to distinguish from squamous cell hyperplastic type lesions. VIN differentiated type, however, has disordered intraepithelial cell maturation involving basal and parabasal areas, with cells having prominent, often localized, increased eosinophilic cytoplasm and nuclear chromatin changes; radial dispersion of chromatin; and prominent nucleoli. Keratin pearl formation may be present. In contrast, squamous hyperplastic lesions have prominent acanthosis without localized changes. Progressive, but not localized, changes may be seen from normal epithelium to the hyperplastic area. There is orderly keratinocytic maturation, without localized basal or parabasal prominent eosinophilic cytoplasm. The nuclei of hyperplastic cells do not have radially dispersed chromatin, but typically have fine chromatin. Nucleoli may be seen and are not a distinguishing feature. Although hypergranulosis and hyperkeratosis are commonly present, keratin pearl formation is not. Differentiated type VIN often expresses p53, although not consistently. Although lichen simplex chronicus (squamous cell hyperplasia) usually does not express p53, such expression does not of itself establish a diagnosis. The presence of associated invasive squamous cell carcinoma contiguous with the focus of suspected differentiated VIN is good evidence to favor differentiated VIN (166,208).

Treatment and Prognosis. Approximately 10 percent of women with VIN have synchronous vulvar invasive squamous cell carcinoma, although higher and lower rates have been reported (61,191,194,442,484). Warty or basaloid VIN is identified adjacent to the corresponding types of invasive carcinoma in approximately 80 percent of cases. The prognosis in these cases is favorable because the majority of the carcinomas are superficial. VIN is found adjacent to invasive squamous cell carcinoma in 55 to 80 percent of cases (101,367,484). Women with invasive carcinoma and coexistent VIN 3 are young, with a mean age of 54 years (423). In contrast, VIN 3 of the differentiated type is usually found adjacent to typical squamous cell carcinomas; the mean age of these women is 77 years (423).

The recurrence of VIN is related to many factors including persistent smoking; however, the status of the margins of excision, when surgical excision is used, also determines the recurrence or persistence rate. In one study, when the lesion extended to the surgical margin, the persistence rate was approximately 20 percent; when the margins were free, the recurrence rate was under 6 percent (126). In another study, half of the patients who had involved margins with surgical excision required further treatment for the VIN within 5 years, whereas only 15 percent of those with clear margins required further treatment (194).

The progression of VIN to invasive carcinoma is well documented. In a retrospective study of 405 women receiving treatment for VIN, 17 (3.8 percent) presented subsequently with invasive vulvar, perianal, or urethral carcinoma (194). Of these, 9 (2 percent) were considered treatment failures and had recurrence averaging 2.4 years after treatment. Eight (1.8 percent) had recurrences, with the squamous cell carcinoma arising in a site separate from the primary tumor. A tumor presented an average of 13.2 years after treatment. In one study in which VIN 3 lesions in five women were biopsied, but not completely excised, progression to invasive squamous cell carcinoma occurred in all five patients (192). A subsequent report on 10 patients without treatment of VIN who subsequently presented with vulvar squamous cell carcinoma did so within 1.1 to 7.3 years of primary diagnosis (194).

Spontaneous regression of VIN has been documented (122,126,193,194). If multiple lesions are present, more than one lesion should be biopsied because the microscopic features may vary from lesion to lesion (463). As in women with condyloma, approximately 30 percent of women with VIN have synchronous or metachronous cervical or vaginal intraepithelial neoplasia, and therefore, examination and subsequent follow-up must include colposcopic examination of the cervix and vagina and cytologic screening for these lesions.

Local excision (partial superficial vulvectomy) is the most common method for treating VIN, and is especially effective in the treatment of small solitary lesions. Electroloop excision, rather than surgical excision, also appears to be effective. Laser ablation is not as effective as either surgical or electroloop excision, although it is an effective alternative to excision (442). Excision has the advantage of providing tissue for microscopic examination to exclude invasion. This is especially important in postmenopausal women with solitary lesions, immunosuppressed patents, and women with Fanconi anemia because of a higher frequency of associated invasive carcinoma (59,61,466). Local excision is also preferred when the lesion is in hair-bearing skin because of the common involvement of skin appendages (389). When multiple or extensive lesions involve nonhair-bearing areas, the treatment can be more superficial provided invasive carcinoma has been excluded by multiple biopsies. VIN in these instances is generally not deeper than 1 mm. Superficial excision by surgical or electroloop excision may be the most effective in such cases, although laser ablation is reported as effective (468). Total or partial superficial vulvectomy is rarely necessary for the treatment of VIN.

Newer promising topical therapies are being explored. Most notably, imiquimod or related type topical immune modulators have been proven to be effective in the treatment of genital condyloma acuminatum. Observation only, after biopsy to establish the diagnosis, may be considered in young women and pregnant women because VIN may regress (123,126). A clinical study has documented the spontaneous regression of VIN 2 and VIN 3 lesions in younger women having papular pigmented lesions (191,193).

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma is an invasive tumor showing squamous differentiation exclusively. Squamous cell carcinoma can be divided into broad categories: 1) squamous cell carcinoma that is stage IA (T1a,N0,M0) and 2) frankly invasive carcinoma that invades to a depth beyond the limits used to define stage IA invasive carcinoma.

Invasive Squamous Cell Carcinoma, Stage IA (T1a,N0,M0)

Definition. *Stage 1A vulvar invasive squamous cell carcinoma* is a primary solitary carcinoma with a depth of invasion of 1 mm or less and a diameter of 2 cm or less, with clinically negative regional lymph nodes and no evidence of metastasis (210,457). The rare presence of vascular space invasion in such superficial tumors does not change the stage above International Federation of Gynecologists and Obstetricians (FIGO) stage IA (T1a,N0,M0) (Table 7-1) (7a).

General Features. Stage IA invasive squamous cell carcinoma of the vulva may present as an ulcer, a red macule or papule, a white hyperkeratotic plaque, or within an area of VIN that may be white, red, brown, or black. No specific findings on clinical examination definitively separate VIN from VIN with invasion (61). Although the staging of vulvar carcinoma lists stage 1A tumors as 2 cm or less in diameter, the vast majority of stage 1A invasive carcinomas are under 2 cm in greatest longitudinal dimension.

Microscopic Findings. The method of measuring "depth of invasion" to define FIGO stage IA vulvar carcinoma requires measurement of the tumor from the epithelial-dermal junction of the most superficial adjacent dermal papilla to the deepest point of invasion (fig. 7-17) (457). The "thickness of the tumor" is defined as the measurement from the surface of the tumor, or the bottom of the granular layer if the surface is keratinized, to the deepest point of invasion. Both thickness and depth of invasion measurements may be of value when the tumor is ulcerated, to distinguish deeply invasive but ulcerated tumors from true stage IA tumors. Ideally, both measurements should be done when possible. In some cases, the depth of invasion cannot be determined with certainty due to various factors, often beyond the pathologist's control. Provided the tumor is not ulcerated, and the entire tumor is resected so that the deepest point of invasion can be determined with reasonable certainty, the thickness of the tumor may be a sufficient measurement, especially when it is apparent that the tumor is thicker

Table 7-1

VULVAR TUMOR PATHOLOGIC STAGING[a]

Primary Tumor (pT)
pTX: Primary tumor cannot be assessed
pT0: No evidence of primary tumor
pTis: Carcinoma in situ (preinvasive carcinoma) (no longer inlcuded in FIGO)
pT1a [FIGO IA]: Lessions 2 cm or less in size, confined to the vulva or perineum, and with depth of stromal invasion 1.0 mm or less[b]
pT1b [FIGO] IB]: Lesions more than 2 cm in size or any size with depth of stromal invasion more than 1.0 mm, confined to the vulva or perineum
pT2 [FIGO II]: Tumor of any size with extension to any adjacent perineal structures including lower/distal 1/3 urethra, lower/distal 1/3 vagina, or anal involvement
pT3 [FIGO IVA]: Tumor of any size with extension to any of the following structures: upper/proximal 2/3 of urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone

Regional Lmph Nodes (pN)
pNX: Regional lymph nodes cannot be assessed
pN0: No regional lymph node metastasis
pN1: Regional lymph node metastasis with the following features:
- N1a: One or two lymph node metastases each less than 5 mm (FIGO IIIA)
- N1b: One lymph node metastasis 5 mm or greater (FIGO IIIA)

pN2: Regional lymph node metastases with the following features:
- pN2a: Three or more lymph node metastases each less than 5 mm (FIGO IIIB)
- pN2b: Two or more lymph node metastases 5 mm or greater (FIGO IIIB)
- pN2c: Lymph node metastasis with extracapsular spread (FIGO IIIC)

pN3: Fixed or ulcerated regional lymph node metastasis (FIGO IVA)

Distant Metastasis (pM)
pM0: No distant metastasis
pM1: Distant metastasis (including pelvic lymph node metastasis) (FIGO IVB)

[a]Data from American Joint Commission on Cancer (AJCC). Cancer staging manual, 7th ed. New York: Springer; 2010, FIGO 2008 Annual Report, and College of American Pathologists, 2010.,
[b]The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

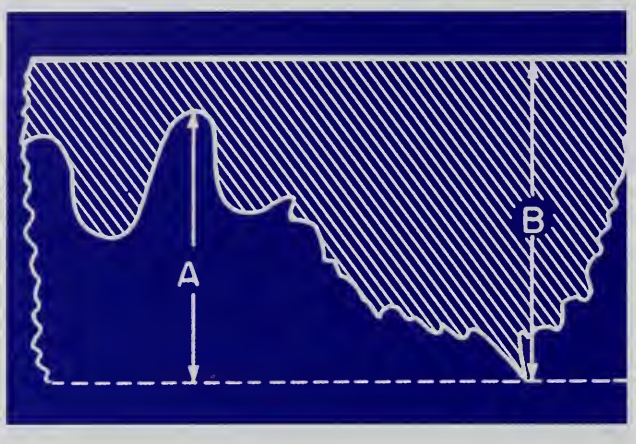


Figure 7-17

MEASUREMENT METHODS FOR SQUAMOUS CELL CARCINOMA OF THE VULVA

The depth of invasion is defined as the measurement from the epithelial dermal junction of the adjacent most superficial dermal papillae to the deepest point of invasion (measurement A). The thickness of the tumor is defined as the measurement from the surface (measurement B). If the surface is keratinized, the measurement is from the base of the granular layer to the deepest point of invasion.

Table 7-2

INFORMATION OF VALUE TO INCLUDE IN THE PATHOLOGY REPORT IN ADDITION TO THE DIAGNOSIS: THE COLLEGE OF AMERICAN PATHOLOGISTS PROTOCOL FOR EXAMINATION OF SPECIMENS FROM PATIENTS WITH VULVAR CARCINOMA[a]

1. The depth of invasion of the tumor, in millimeters
2. The thickness of the tumor
3. The method of measurement of the depth of invasion and thickness of the tumor
4. The presence or absence of vascular space involvement by the tumor
5. The diameter of the tumor, including the clinically measured diameter if available

[a]Data from reference 457.

than 1 mm. The methods used to measure the tumor should be specified in the pathology report (Table 7-2) (457). Stage IA invasive squamous cell carcinoma is discussed separately from frankly invasive squamous carcinoma in this presentation.

Microscopic features that assist in identifying squamous cell carcinoma arising in VIN, or in differentiated VIN, include the following: 1) isolated neoplastic squamous cells with increased eosinophilic cytoplasm and atypical nuclei with prominent nucleoli in the stroma; 2) loss of the usual palisaded arrangement of the basal keratinocytes of the dermal papillae; 3) small irregularly shaped nests of neoplastic squamous cells with disorderly orientation within the dermis; 4) dyskeratosis and keratin pearl formation; and 5) a reaction in the dermis characterized by fibrosis or edema localized to the area of invasion (figs. 7-14, 7-18–7-20). Immunoreactive laminin surrounds nests of VIN whereas it is discontinuous around invasive nests of epithelium (102). Although laminin may facilitate the recognition of invasion, too few cases have been studied to recommend it for clinical use at the present time.

Treatment and Prognosis. The risk of lymph node metastasis in women with a solitary stage IA (T1a,N0,M0) invasive squamous cell carcinomas (depth of invasion less than 1 mm) is zero in large series where the depth of invasion has been well defined (11,49,101,159,160,186,367, 458,459,467,477). A study of 40 women with stage T1 vulvar carcinoma with depth of invasion of 1 mm or less, with a mean follow-up 7.6 years, revealed that 1 of the 10 patients who had groin lymphadenectomy had groin metastasis (246). One of 30 patients who did not have groin dissection had a groin metastasis 7.5 years following surgical treatment. In a recent study, 26 of 28 women with stage 1A vulvar squamous cell carcinoma were treated with wide local excision, and 2 patients were treated with more extensive surgery (477). None of these patients died of recurrent disease or metastatic carcinoma after long-term follow-up. According to the data presented here, the only histologic feature for predicting concurrent lymph node metastasis is tumor depth of invasion.

Therapy for women with stage IA (T1a,N0,M0) vulvar carcinoma is wide local excision (partial vulvectomy) without ipsilateral inguinal-femoral lymph node dissection (48,97,159,459).

Invasive Squamous Cell Carcinoma, Stage IB (T1b and Higher)

General Features. Squamous cell carcinoma accounts for approximately 95 percent of malignant tumors of the vulva and 3.5 to 8.0 percent of those of the female genital tract (10,483). The incidence in the United States is 1.5/100,000 women per year and increases with age; the mean age at presentation is between 60 and 74

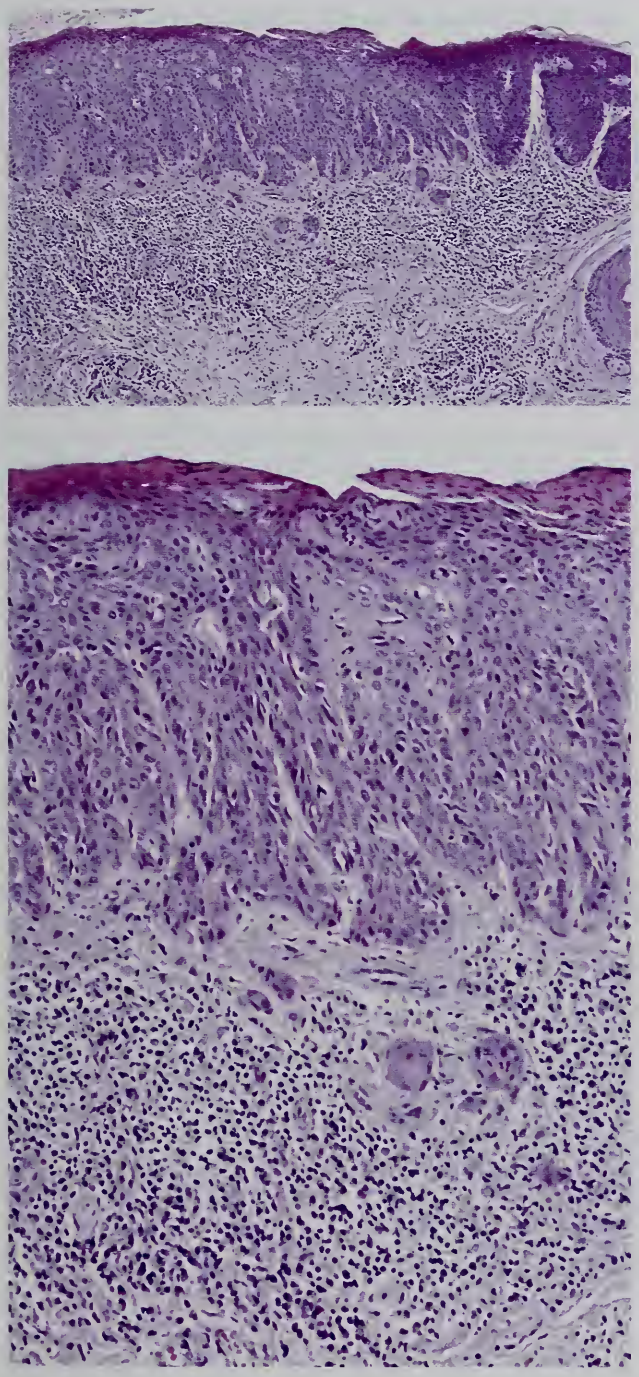


Figure 7-18

STAGE IA INVASIVE SQUAMOUS CELL CARCINOMA WITH HIGH-GRADE VIN

Top: The invasive squamous cell carcinoma is contiguous with the high-grade VIN. The orderly palisaded arrangement of the epithelial cells at the epithelial-dermal junction is lost, and small foci of squamous cell carcinoma are seen within the superficial dermis. There is an associated moderate mixed chronic inflammatory cell dermal infiltrate.

Bottom: Higher magnification shows a loss of the palisade arrangement of the basal keratinocytes at the point of dermal invasion. Some small clusters of tumor cells are present in the dermis underlying the focus of invasion.

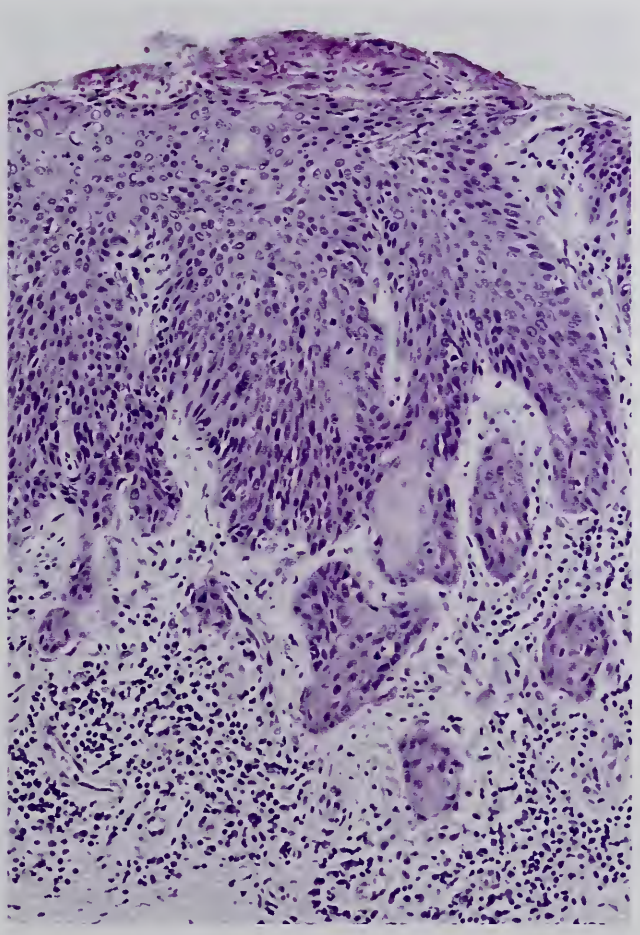


Figure 7-19

INVASIVE SQUAMOUS CELL CARCINOMA WITH A DEPTH OF INVASION OF 1.2 MM

This tumor is associated with high-grade VIN. The neoplastic keratinocytes in the focus of invasion have some increase in eosinophilic cytoplasm. There is a marked inflammatory response.

years (160,175). Vulvar carcinoma, however, may occur in younger women, and has been described in a 12-year-old girl (341).

The epidemiology of vulvar squamous cell carcinoma is not as well delineated as that of cervical carcinoma, but there is a recognized increased risk with a history of VIN, lichen sclerosus, condyloma acuminatum, cervical carcinoma, advancing age, number of lifetime sexual partners, cigarette smoking, immunodeficiency, poor perineal hygiene, and genital granulomatous disease (37,351,387). An increased risk has been identified in women working in cotton mills, related to exposure to industrial oils, as well as those working in the dyeing and cutlery industries. Blood group A has

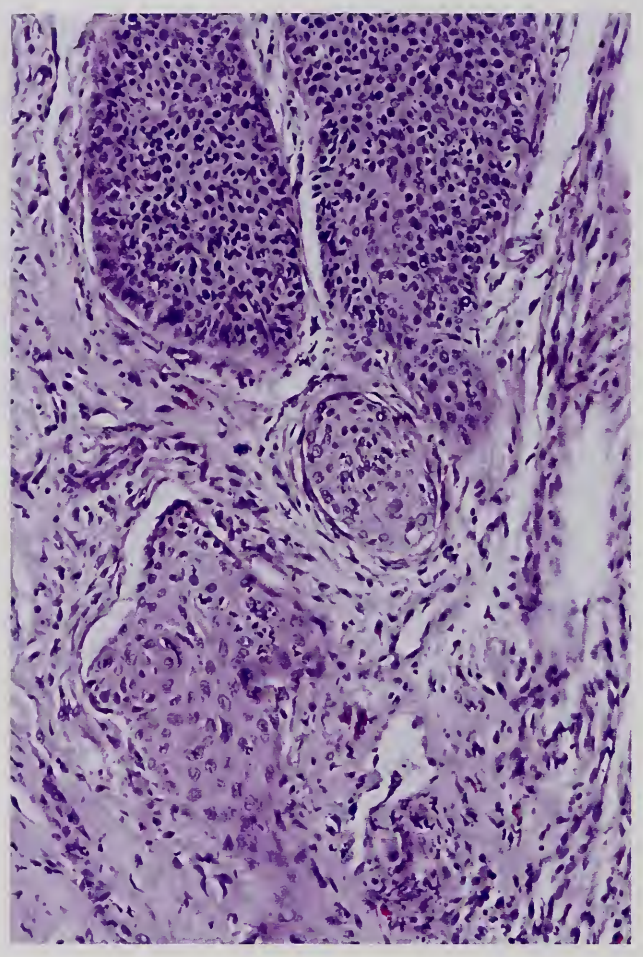


Figure 7-20

FOCAL INVASIVE SQUAMOUS CELL CARCINOMA WITH VIN 3

The overlying high-grade VIN, basaloid type, is contiguous with the invasive squamous cells. The eosinophilic cytoplasm and nuclear pleomorphism are increased in the invasive keratinocytes, with loss of nuclear hyperchromasia and prominent nucleoli. Some chronic inflammatory cells are present in the surrounding dermis.

been studied as a possible risk-associated factor, but results remain inconclusive (351).

There are reported differences between young and older women in the distribution of HPV in invasive squamous cell carcinomas. HPV, generally type 16, is found in only 21 percent of vulvar carcinomas in older women (mean age, 77 years) compared to 81 percent of younger women (mean age, 50 years). The histologic features of the invasive carcinoma differ as well. The neoplasms in older women have the typical appearance of squamous cell carcinoma, usually being well differentiated and highly keratinized, whereas the tumors in younger women are usually of the basaloid or warty type (218,350,423).

Clinical Features. The most common symptoms of patients with squamous cell carcinoma are pruritus, pain, discharge, bleeding, dysuria, and foul odor. The tumor may arise anywhere on the vulva but the labia majora, labia minora, and clitoris are the most common sites (figs. 7-21, 7-22). The clitoris is the primary site in 5 to 15 percent of the cases (10,159,186). The perineal body and posterior fourchette are the primary sites in approximately 15 percent of the cases (483). The carcinoma is solitary in about 90 percent of the cases, and is over 2 cm in diameter in at least 60 percent (101,247,447).

VIN is infrequently found adjacent to the typical (keratinized) invasive squamous cell carcinoma. When present, it is the differentiated (simplex) type of VIN. Lichen sclerosus is not considered an intraepithelial neoplastic process. Nonetheless, it is recognized that women with longstanding lichen sclerosus, especially those with associated squamous hyperplastic lesions or differentiated VIN, are at risk for squamous cell carcinoma arising within the area of lichen sclerosus (fig. 7-21) (101,363,367,476,484). In these cases, the adjacent vulvar epithelium is thickened and gray-white due to intraepithelial edema or hyperkeratosis. The invasive carcinoma presents as a focally hyperkeratotic area, ulcer, nodule, or ulcerated mass (168,484). The lifetime risk of vulvar carcinoma in women with lichen sclerosus is unknown, however, the frequency has been reported to be 3.6 percent in one study and the estimated lifetime risk in this population may be 20 percent or higher (56). A review of a cohort of women with vulvar lichen sclerosus reported that 9 percent subsequently presented with VIN, and 21 percent with vulvar squamous cell carcinoma (56). Vulvar carcinoma presented as early as 1 and as late as 23 years (mean, 4 years) after the onset of symptoms. In a retrospective evaluation of vulvectomy specimens from women with vulvar squamous cell carcinoma, the frequency of identifying lichen sclerosus associated with squamous cell carcinoma ranged from 15 to 40 percent, the higher rate being observed in deeply invasive squamous carcinomas (483,485). Squamous cell carcinomas associated with lichen sclerosus involving the vulva are

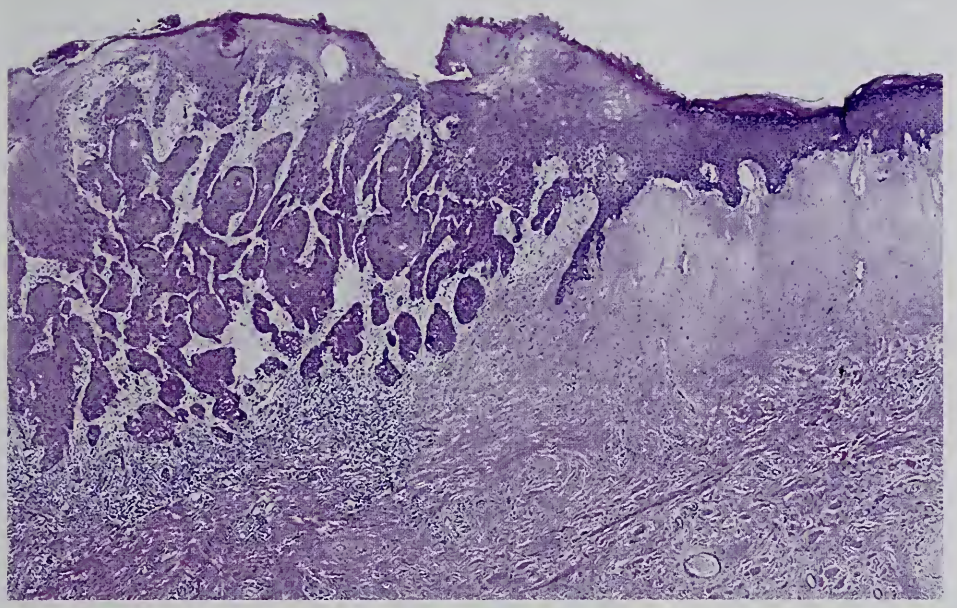


Figure 7-21

LICHEN SCLEROSUS WITH ASSOCIATED SQUAMOUS CELL CARCINOMA

Invasive squamous cell carcinoma is immediately adjacent to lichen sclerosus. The dermis just below the lichen sclerosus is edematous and hypocellular.

Figure 7-22

EXOPHYTIC SQUAMOUS CELL CARCINOMA

The tumor involves the left labia minus and majus and involves the vestibule. It has an ulcerated surface and protrudes from the adjacent epithelium.

usually of the large cell, keratinizing type and lack association with HPV infection.

Rarely, squamous cell carcinoma arises in association with a granulomatous lesion of the vulva such as granuloma inguinale (387). Carcinoma also has been reported in young women who are immunosuppressed in association with renal transplantation (59).

Gross Findings. Invasive squamous carcinoma may be an ulcerated, exophytic, or papillomatous mass. Squamous cell carcinomas are usually solitary, but are multifocal in approximately 10 percent of the cases (483). The tumor is most commonly located on the labia minora or majora, in the transitional area from the nonkeratinized epithelium of the vulvar vestibule to the adjacent keratinized epithelium.

Microscopic Findings. Squamous cell carcinomas of the vulva are usually one of three types: squamous cell carcinoma of the usual type, which may be keratinizing or nonkeratinizing; warty (condylomatous) carcinoma; or basaloid carcinoma. Other types have been reported as well (Table 7-3).

Squamous Cell Carcinoma of the Usual Type. Squamous cell carcinoma of the usual type is composed entirely of neoplastic squamous epithelial cells, and is subclassified as keratinizing or nonkeratinizing. Keratinization includes dyskeratotic cells, parakeratotic cells, or keratin pearls. When keratinization is present, without features of warty carcinoma, the tumor is classified as keratinizing type (fig. 7-23). These tumors may be associated with HPV.

Squamous cell carcinomas associated with lichen sclerosus are of the usual type, and are often keratinizing. The tumor suppressor gene product p53 is expressed in approximately half the cases and cytokine tumor growth factor (TGF)-beta in one third as compared to 19 percent and 9 percent of the respective usual HPV-related carcinomas (i.e., warty and basaloid squamous cell carcinomas). Squamous cell carcinomas associated with lichen sclerosus are associated with a prominent fibromyxoid dermal response in about half of the cases. *p53* mutation and clonal studies do not support suggestions that squamous hyperplasia of the vulva is a precursor of vulvar squamous carcinoma (208,476).

Confluent growth, defined as anastomosing cords of invasive tumor that exceed 1 mm in diameter, is a characteristic of more deeply invasive squamous cell carcinomas (320,459). In evaluating tumors with a depth of invasion beyond 1 mm, the tumor growth pattern appears to have some influence on lymph node metastasis. Tumors with a compact or pushing pattern of growth are less likely to metastasize than tumors with a diffuse or finger-like pattern of infiltrative growth. Tumors with a depth of invasion exceeding 2 mm with vascular space involvement have a significantly higher association with nodal metastases than tumors without vascular invasion (336).

Microscopic Grading. The grading system recommended by the American Joint Committee on Cancer (AJCC) for vulvar carcinoma is as follows: GX: grade cannot be assessed, G1: well-differentiated, G2: moderately differentiated, G3: poorly differentiated, and G4: undifferentiated (7a).

Table 7-3

HISTOPATHOLOGIC TYPES OF VULVAR SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma, keratinizing type
Squamous cell carcinoma, nonkeratinizing type
Basaloid carcinoma
Warty (condylomatous) carcinoma
Verrucous carcinoma
Acantholytic squamous cell carcinoma
Squamous cell carcinoma with tumor giant cells
Spindle cell carcinoma

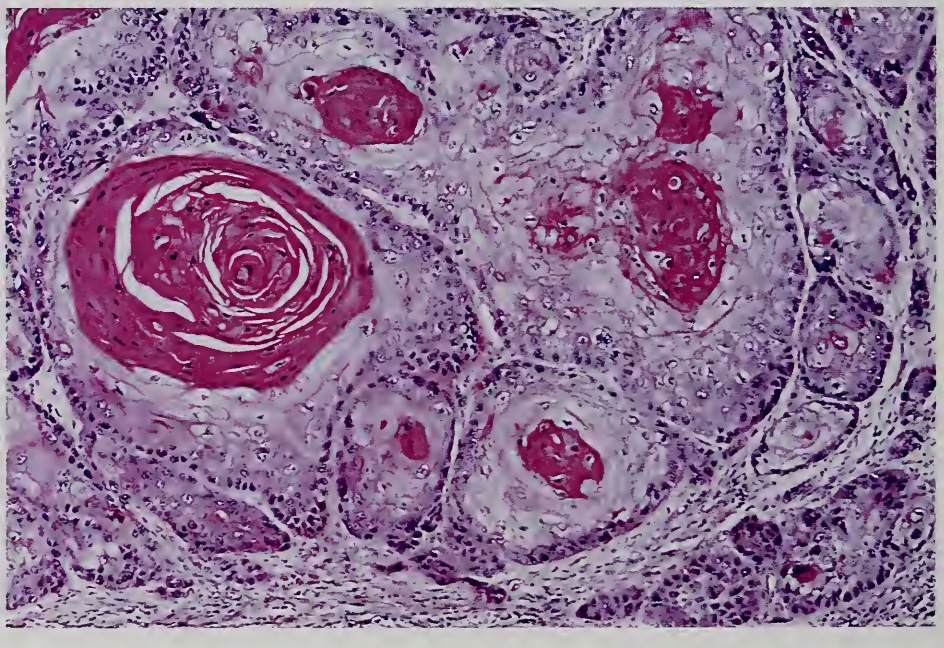


Figure 7-23

KERATINIZING, WELL-DIFFERENTIATED SQUAMOUS CELL CARCINOMA

The tumor cells are large, with uniform nuclei and abundant eosinophilic cytoplasm. Keratin pearls are present.

The Gynecologic Oncology Group (GOG) has advised grading squamous cell carcinomas according to the percentage of undifferentiated cells (176a). The latter are small cells with scant cytoplasm showing little or no differentiation and infiltrating the stroma either in elongated cords or small clusters. This grading system can be reduced to three grades (196): grade 1 tumors have no undifferentiated cells, grade 2 tumors have undifferentiated cells comprising less than half of the tumor, and grade 3 tumors contain half or more of the poorly differentiated component. Grade 1 tumors have little risk of regional lymph node metastasis; the risk is higher with increasing grade. Currently, tumor grading is not routinely performed in most laboratories.

Histopathologic Findings that Correlate with Prognosis. Clinical pathologic studies have shown that the following features correlate with prognosis and therefore should be included in the surgical pathology report: 1) the depth of invasion in millimeters (see fig. 7-17); 2) the thickness of the tumor in millimeters; 3) the presence or absence of vascular space involvement by the tumor; 4) the diameter of the tumor (as measured from the specimen in the fresh or fixed state); 5) the clinical measurement of the tumor diameter, as measured in the patient, including whether it involves contiguous sites; and 6) the presence of lymph node metastasis, or other metastasis (Table 7-2) (457). Tumors with a depth of invasion of beyond 1 mm and higher stage (grade 3 tumors) are generally associated with a higher frequency of vascular space invasion, lymph node metastasis, higher recurrence rate, and poorer survival (176a,477). In a recent study of stage 1B and stage 2 vulvar squamous cell carcinomas, the only histologic feature for predicting concurrent lymph node metastasis is tumor depth of invasion (477). For predicting recurrence in women with stage 1 and stage 2 vulvar squamous cell carcinoma, the three most important histologic features are: 1) the depth of invasion of the tumor, 2) the presence of squamous cell carcinoma at the surgical margins, and 3) the histologic grade of the tumor (fig. 7-24).

A univariate analysis of 108 patients with vulvar carcinoma demonstrated the following features to be associated with better survival: tumor size under 2 cm in greatest dimension, depth of invasion of 1 mm or less ($p<0.01$), tumor thickness of 5 mm or less, no evidence of lymph node metastasis as determined by histopathologic examination ($p<0.01$), and adjacent VIN 3, excluding VIN 3 of the differentiated type ($p<0.02$) (371). In a study of 215 patients with vulvar squamous cell carcinoma, the finding of tumor at excision margins or tumor with depth of invasion beyond 5 mm significantly increased the risk of local recurrence (370). In this study, local recurrence of the tumor at the primary site was associated with a significant risk of cancer-related death, whereas the occurrence of a second squamous carcinoma at a distant site on the vulva did not influence survival.

A multivariate analysis has demonstrated that tumors that are FIGO stage II or higher, are present in inguinal femoral lymph nodes, and have vascular space involvement are associated with a higher rate of recurrence than tumors without such findings (245,370).

Immunohistochemical Findings. Immunohistochemical studies reveal that most squamous cell carcinomas of the vulva contain both high and low molecular weight keratins (229,419). Evidence of alterations in the p16/pRb/cyclin D1 pathway in vulvar squamous cell carcinoma, studied by molecular genetics methods, demonstrated that vulvar squamous cell carcinoma commonly has evidence of epigenetic silencing of p16 INK4 (seen in two thirds of 38 cases studied) (232). Approximately one fifth of the cases had overexpression of cyclin D1, and one fifth lacked pRb protein. In another study, expression of pRB2/p130 was lost in 57 percent of 51 vulvar carcinomas and in 1 of 7 (14 percent) VIN lesions (487). In addition, loss of p27kip1 was observed in 31 percent of the invasive carcinomas, in 1 of 7 (14 percent) VIN lesions, and in 2 of 18 (11 percent) adjacent nonneoplastic epithelial disorders. Significant loss of expression of both suppressor genes *pRB2/p130* and *p27(kip1)* is found in vulvar squamous cell carcinoma as compared to VIN (487).

Differential Diagnosis. The differential diagnosis of squamous cell carcinoma includes malignant melanoma, especially the amelanotic type, metastatic squamous cell carcinoma, epithelioid sarcoma, epitheliomatous hyperplasia, keratoacanthoma, inverted follicular keratosis, skin appendage involvement by VIN, and vulvar amyloidosis.

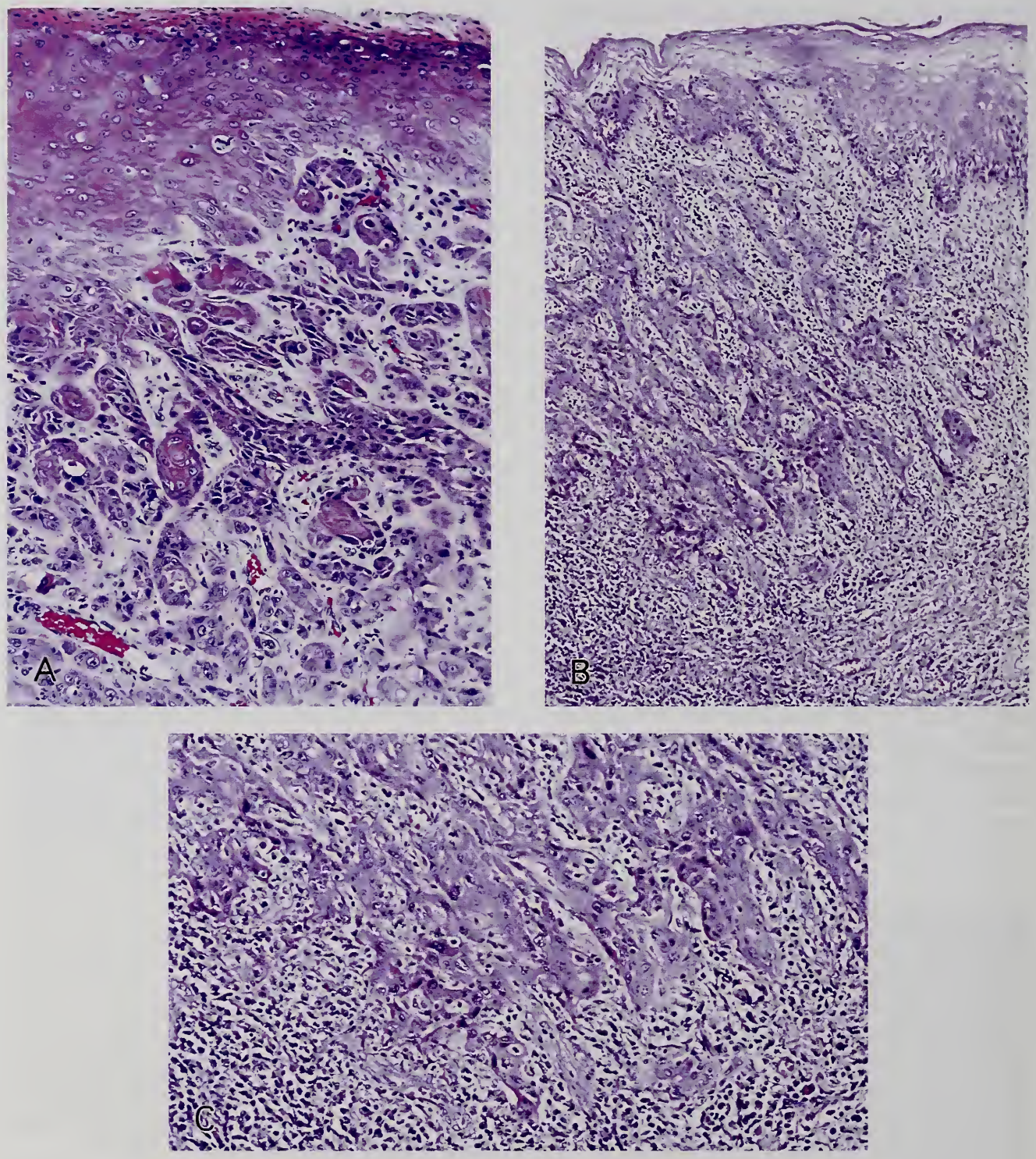


Figure 7-24

NONKERATINIZING, POORLY DIFFERENTIATED SQUAMOUS CELL CARCINOMA, WITH A DIFFUSE, TENTACULAR (SPRAY) INFILTRATIVE PATTERN OF INVASION

A: The tumor is associated with dermal desmoplasia. A moderate chronic inflammatory infiltrate is peripheral to the desmoplastic dermal reaction.

B: This tumor invades the submucosa of the vulvar vestibule. Overlying is glycogen-rich squamous mucosa. There is a moderate mixed chronic inflammatory cell infiltrate associated with the tumor.

C: High magnification shows a diffuse infiltrative pattern without keratin formation. There is a moderate chronic inflammatory cell infiltrate.

Malignant melanomas contain immunoreactive S-100 protein antigen, HMB45, and Melan-A, and lack keratin. In addition, melanomas may have a superficial spreading or intraepithelial melanoma adjacent to the invasive component of the tumor. Metastatic squamous cell carcinomas, usually from the cervix or anus, tend to involve deeper tissues and lymphatics without an adjacent intraepithelial component or transition from the adjacent surface epithelium.

Epithelioid sarcomas may resemble nonkeratinizing squamous cell carcinoma and have similar immunohistochemical findings. They are distinguished by their granuloma-like appearance; location, which is typically deep and adjacent to fascia; and lack of an intraepithelial neoplastic component.

Pseudoepitheliomatous hyperplasia is composed of nests of bland-appearing squamous cells. At the margin of the nests, a palisaded arrangement of the basal cells is often retained. In contrast, carcinomas have more irregularly shaped jagged edges and tumor nests containing cells with greater nuclear atypia. Granular cell tumors in particular may be associated with overlying pseudoepitheliomatous hyperplasia (471). Prior biopsy sites may also contain embedded epithelium and therefore simulate carcinoma; however, the epithelium is normal appearing and lacks infiltrative features. In addition, there may be foreign body giant cells containing suture material.

Keratoacanthomas have a distinctive hyperkeratotic central core and an infiltrative pattern that converges inwardly or centrally. Despite the infiltrative pattern, the tumor-dermal interface is well defined in contrast to the irregular border of squamous cell carcinoma. Inverted follicular keratosis may have a pseudoinfiltrative growth pattern; however, the epithelial cells lack significant atypia or mitotic counts over 1 to 2 per 10 high-power fields, although squamous eddies may be present. The adjacent epithelium lacks evidence of VIN, and the adjacent dermis lacks desmoplasia (369).

Skin appendage involvement by VIN may mimic invasive squamous cell carcinoma, especially in the tangentially sectioned specimen. Unlike squamous cell carcinoma, VIN retains the orderly arrangement of the epithelial cells along the basement membrane, does not have cellular differentiation, and is not associated with stromal desmoplasia or edema. Multiple sections usually reveal identifiable skin appendage epithelium in continuity with the intraepithelial neoplastic cells (see Vulvar Intraepithelial Neoplasia). Vulvar amyloidosis has been described which clinically resembled carcinoma, but was readily distinguished on biopsy by the presence of amyloid in the superficial dermis of the vulvar mass (326).

Clinical Behavior. Vulvar squamous cell carcinoma spreads locally, by lymphatics and blood vessels. It commonly extends to the vagina and the distal urethra, and in advanced cases, to the base of the bladder, pelvic bones, and perirectal tissues. A study of 502 recurrences of vulvar squamous cell carcinoma by site found 53.4 percent recurring in the perineal area, 18.7 percent with inguinal recurrence, 5.7 percent with pelvic recurrence, 7.9 percent with distant metastasis, and 14.2 percent with multiple metastatic sites (245). Recurrence at the site of the primary tumor carries a significant risk for cancer-related death. The occurrence of a second squamous cell carcinoma at another vulvar site, however, is not associated with a similar tumor mortality risk (370). Vascular space invasion increases the probability of lymph node metastasis when the depth of invasion exceeds 1 mm (49,186,219). The ipsilateral superficial inguinal and femoral nodes are most commonly involved; however, contralateral lymph node metastasis also occurs. When the superficial inguinal-femoral nodes are free of tumor, there is essentially no risk of deep pelvic lymph node involvement and little risk of deep femoral node metastasis. When these superficial nodes contain tumor, however, approximately 25 percent of the patients have deep pelvic lymph node involvement because these nodes drain the superficial inguinal nodes (97). The most proximal superficial node, the node of Cloquet (or Rosenmüller), is commonly sampled at the time of vulvectomy since its involvement mandates treatment of the deep pelvic nodes. The medial external iliac nodes drain the superficial inguinal nodes and deep femoral nodes, and are the most common lymph nodes involved when the more superficial nodes contain tumor. The lateral external iliac nodes are infrequently involved. Tumor from the deep pelvic nodes may metastasize

to the paraaortic nodes and enter the thoracic duct and the venous circulation, leading to metastasis to the supraclavicular nodes, lung, liver, and other remote sites. Distant spread occurs as a result of direct venous invasion.

Staging. The 2010 FIGO staging system for vulvar carcinoma is shown in Table 7-1. Sentinel lymph node mapping is used for planning the extent of inguinal-femoral lymphadenectomy. If the sentinel lymph node or nodes are negative by histopathologic examination, the inguinal-femoral lymph nodes can be left intact. If the sentinel lymph nodes contain metastasis, additional inguinal-femoral lymphadenectomy, or other therapy, may be needed. Sentinel lymph node sampling often employs 99mTc (CIS-US, Bedford, Mass)-labeled colloid and a hand-held gamma detection device. Isosulfan blue dye injection (1 percent aqueous Isosulfan Blue)(Zenith Parenterals, Rosemant, Ill.) is an alternative. Both methods may be used together to detect sentinel lymph nodes in vulvar carcinoma patients (89,275). This methodology appears promising in reducing the need for extended inguinal-femoral lymphadenectomy in women with vulvar carcinoma.

Treatment. Squamous cell carcinomas that have a depth of invasion exceeding 5 mm, and those that are stage II to stage IVA, are usually treated by partial or total deep vulvectomy with bilateral superficial inguinal-femoral lymph node dissection (219). In selected cases (tumors 1 to 3 cm in diameter, without suspicious inguinal-femoral lymph nodes), partial deep vulvectomy with ipsilateral superficial inguinal-femoral lymphadenectomy has similar clinical results as bilateral lymphadenectomy, but with decreased surgical morbidity (143a). If the superficial nodes, including the Cloquet node, are free of tumor, no additional therapy is indicated. If the superficial inguinal-femoral nodes, or Cloquet node, are involved by metastatic tumor, the deep pelvic nodes are usually treated by postoperative pelvic radiotherapy. Most superficial stage I tumors are treated by a more conservative operation, usually wide local excision or partial deep vulvectomy, with ipsilateral or bilateral inguinal-femoral lymphadenectomy.

Prognosis. Survival is primarily related to the stage of the disease. Women with tumor of 1 mm in depth of invasion or less are almost always cured, although the occurrence of a second primary vulvar carcinoma (referred to as a reoccurrence in contrast to recurrence), has been described in such patients (467). Patients with a stage I carcinoma have a mean 5-year survival rate of 85 percent; those with stage II, 60 percent; stage III, 40 percent; and stage IV, 10 percent.

Basaloid Carcinoma

General Features. Recent studies have shown an elevated prevalence of HPV, mainly type 16, with certain types of invasive squamous cell carcinoma of the vulva. Among these are *basaloid carcinomas*, which occur in young women (mean age, 54 years) rather than typical keratinizing squamous cell carcinomas (mean age, 77 years). Basaloid carcinomas are associated with adjacent VIN in approximately three quarters of the cases, usually of the basaloid type. In contrast to typical squamous cell carcinomas, approximately one quarter of basaloid carcinomas are associated with synchronous or metachronous squamous neoplasms of the cervix and/or vagina (218).

Gross Findings. On gross examination, basaloid carcinomas are similar to typical squamous cell carcinomas.

Microscopic Findings. Basaloid carcinomas are characterized by variable-sized nests of immature squamous cells showing little, if any, squamous maturation (figs. 7-25, 7-26). Some tumors are composed of small, irregularly shaped clusters and cords of cells surrounded by a densely hyalinized stroma. The basal type cells within the nests and cords resemble those in the classic type of carcinoma in situ of the cervix. Characteristically, they are ovoid and uniform in size, with scant cytoplasm and a high nuclear-cytoplasmic ratio, and therefore, they appear undifferentiated. Nuclei contain evenly distributed, coarsely granular chromatin, creating a stippled appearance. A moderate degree of mitotic activity is usually evident. Occasionally, the cells in the center of a nest show evidence of maturation and contain more abundant cytoplasm. Keratinization may be evident in the center of the nests and keratin pearls are occasionally present. Desmosomes are usually not evident.

Differential Diagnosis. Basaloid carcinoma may at times be difficult to distinguish from basal cell carcinoma. In contrast to basaloid

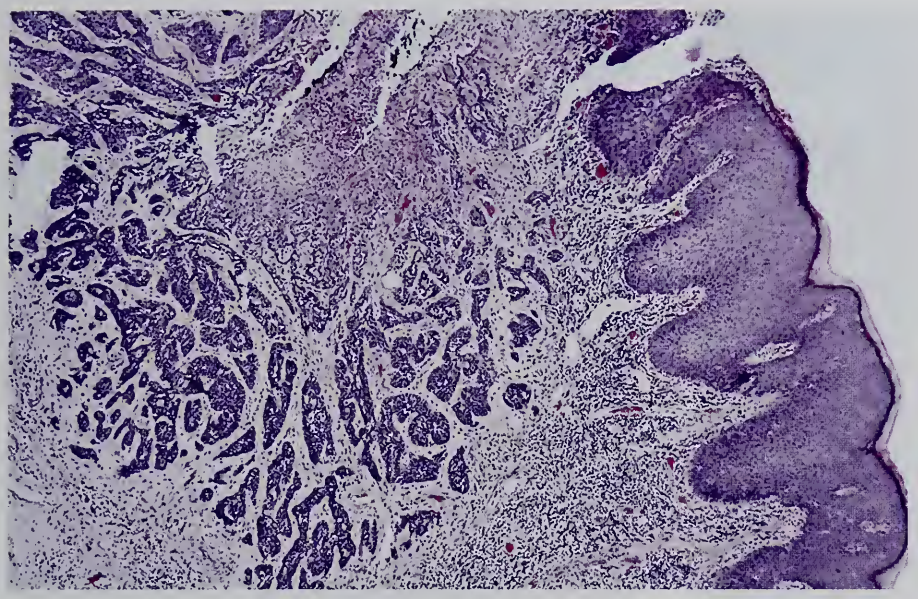


Figure 7-25

BASALOID VIN WITH BASALOID SQUAMOUS CELL CARCINOMA

The tumor is composed of uniform neoplastic squamous cells with hyperchromatic nuclear chromatin. The dermis immediately adjacent to the tumor is somewhat desmoplastic, with a moderate chronic inflammatory cell response.

carcinoma, basal cell carcinomas tend to be more circumscribed and have a lobular appearance. The characteristic palisading of the outermost layer of cells in the nests of basal cell carcinoma is lacking in basaloid carcinoma. Basal cell carcinomas also express BerEP4 (416).

Other entities in the differential diagnosis of basaloid carcinoma are metastatic small cell carcinoma (peripheral neuorendocrine carcinoma) and Merkel cell tumor. These tumors have a more diffusely infiltrative pattern characterized by ill-defined nests, trabeculae, and individual cells invading the stroma rather than the broad anastomosing bands and well-defined nests typical of basaloid carcinoma. Immunohistochemistry is of use in distinguishing these tumors. Small cell tumors of neuroendocrine origin usually express neuroendocrine markers. Merkel cell tumors express a distinctive perinuclear immunoreactive "dot" with cytokeratin, especially CK20.

Treatment and Prognosis. The behavior of basaloid carcinoma appears to be similar to that of typical keratinizing squamous cell carcinoma but there is insufficient experience at this point to draw firm conclusions. Treatment is the same as for squamous cell carcinoma of the usual type (218).

Warty (Condylomatous) Carcinoma

General Features. This type of squamous cell carcinoma is associated with HPV, particularly type 16, and occurs in younger women (218). The gross appearance may resemble verrucous

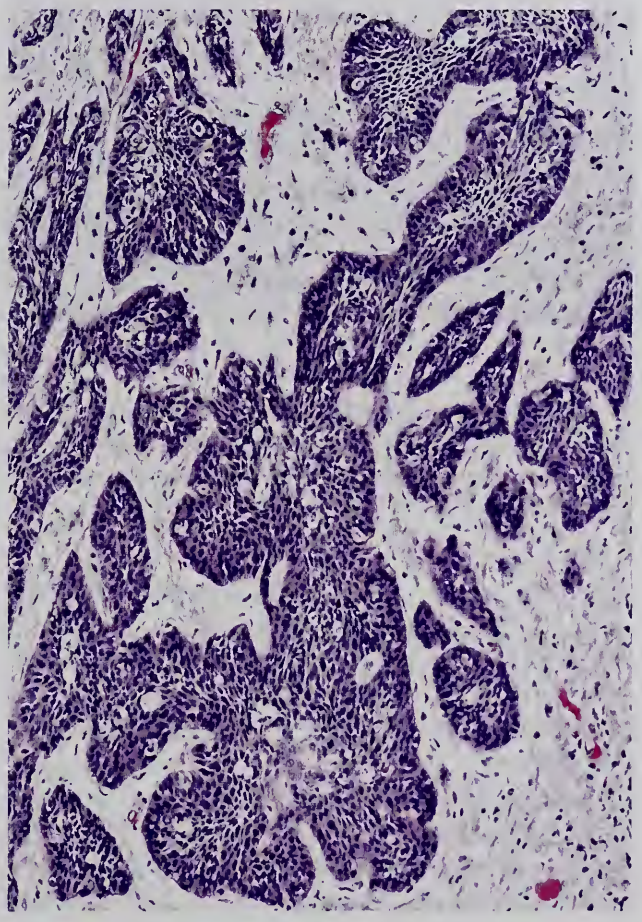


Figure 7-26

BASALOID SQUAMOUS CELL CARCINOMA

The tumor is composed of immature-appearing neoplastic squamous cells that have minimal nuclear pleomorphism but prominent nuclear hyperchromasia. Koilocytosis is not present. The dermal inflammatory response consists predominately of lymphocytes.

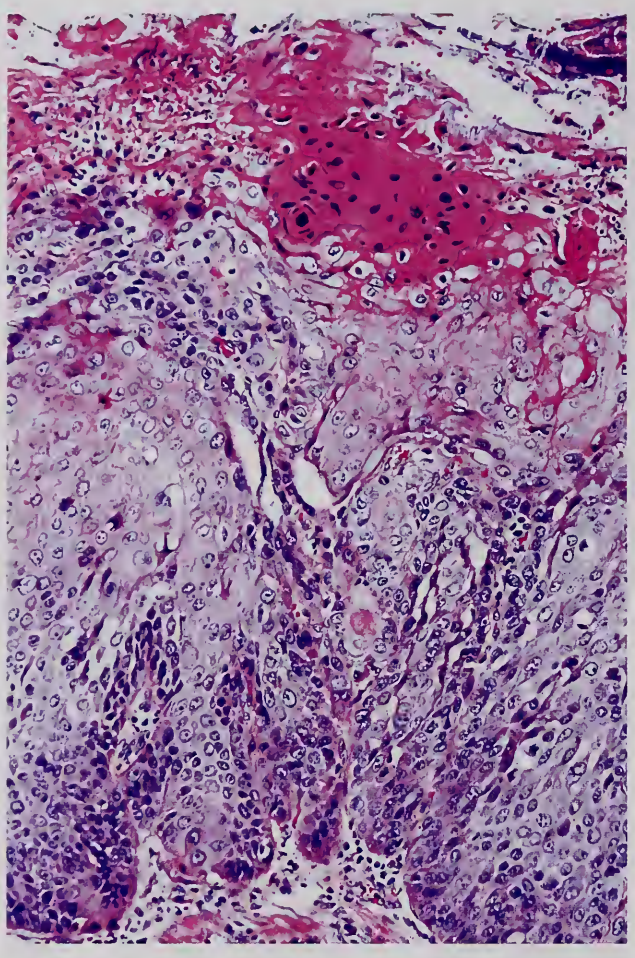


Figure 7-27

WARTY (CONDYLOMATOUS) VIN ASSOCIATED WITH WARTY CARCINOMA

The VIN has a verruciform, hyperkeratotic surface with prominent dermal papillae.

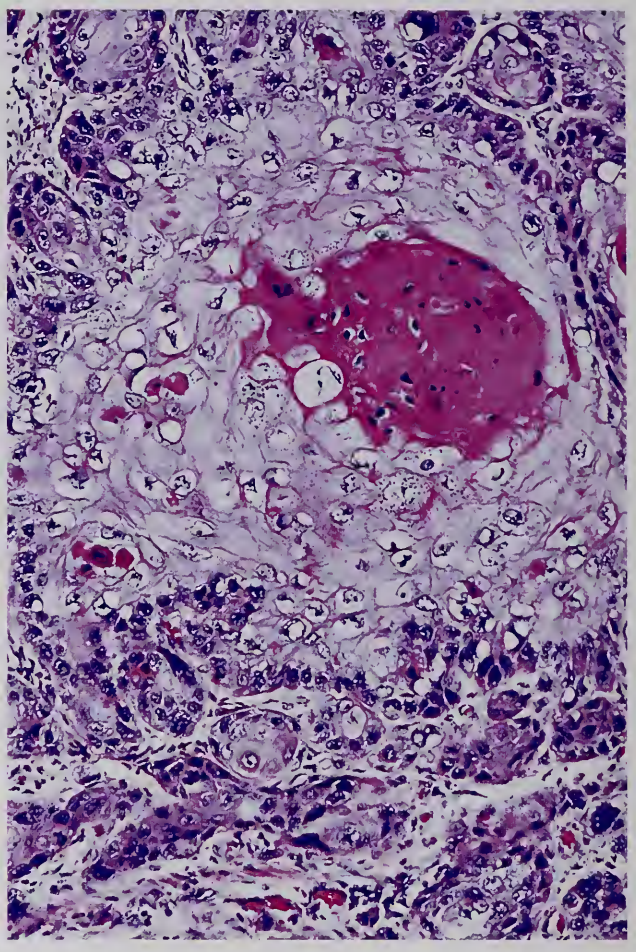


Figure 7-28

WARTY (CONDYLOMATOUS) CARCINOMA

The neoplastic squamous cells have abundant eosinophilic cytoplasm, moderate nuclear pleomorphism, and focal koilocytosis.

carcinoma: large and exophytic with a papillary appearance. Based on the striking verruciform features and associated morphologic features of HPV infection, including koilocytosis, the tumor has been designated *warty* or *condylomatous carcinoma* (98,350).

Microscopic Findings. The surface of the tumor is papillary and covered by hyperkeratotic squamous epithelium that has some features of HPV infection and may include koilocytosis, keratinocyte multinucleation, prominent intracellular bridges, and other features. Dermal fibrovascular cores support the papillary-like surface epithelium (fig. 7-27). At the deep tumor-dermal interface, the tumor is composed of jagged, irregularly shaped nests of epithelial cells (fig. 7-28). Squamous pearls, similar to those found in well-differentiated squamous cell carcinoma, may be present. The individual squamous cells of warty carcinoma, however, display nuclear pleomorphism and cytologic atypia ranging from mild to marked. The nuclear changes are characterized by enlargement, wrinkling of the nuclear membrane, hyperchromasia, and occasional multinucleation. Approximately three quarters of warty carcinomas have adjacent warty and/or basaloid VIN. About one quarter are associated with other genital tract squamous cell neoplasms (218).

Differential Diagnosis. The differential diagnosis includes verrucous carcinoma and typical keratinizing squamous cell carcinoma. The presence of large numbers of cells displaying koilocytotic atypia is a characteristic feature of

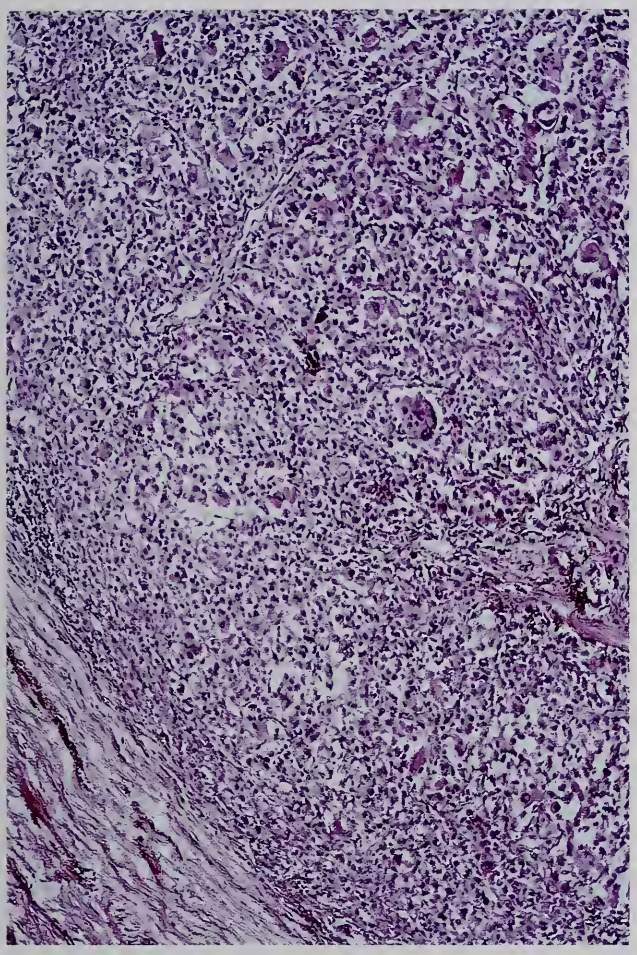


Figure 7-29

SQUAMOUS CELL CARCINOMA WITH TUMOR GIANT CELLS

The neoplastic squamous cells are large, contain abundant cytoplasm, and have large multiple nuclei with prominent nucleoli.

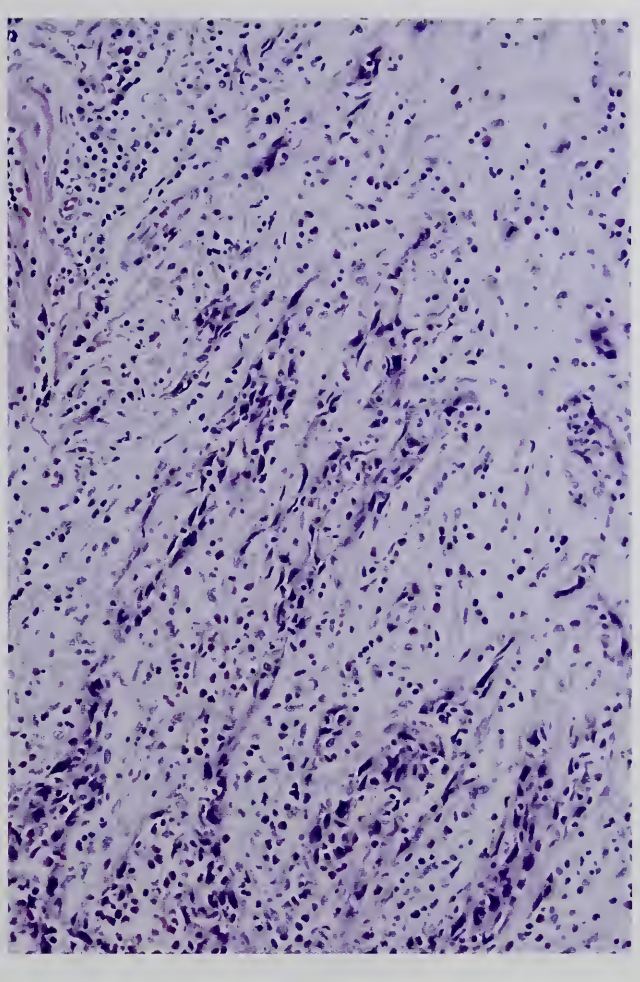


Figure 7-30

SPINDLE CELL SQUAMOUS CELL CARCINOMA

The spindle-shaped cells have pleomorphic nuclei. There is moderate stromal desmoplasia with a minimal chronic inflammatory infiltrate.

warty carcinoma and assists in the distinction of this tumor from keratinizing squamous cell carcinoma and verrucous carcinoma. Keratinizing squamous cell carcinoma occasionally contains a few cells showing koilocytotic atypia but not the large numbers seen in warty carcinoma; verrucous carcinoma does not display koilocytotic atypia.

Treatment and Prognosis. The treatment is the same as for squamous cell carcinoma of the usual type. Although experience with this tumor is limited, it appears that the prognosis falls between that of verrucous carcinoma and typical squamous cell carcinoma, and is generally good. Lymph node metastasis, however, is occasionally observed (218).

Squamous Cell Carcinoma with Tumor Giant Cells

Squamous cell carcinoma with tumor giant cells is a variant of squamous cell carcinoma that is usually nonkeratinizing and consists of multinucleated tumor cells (fig. 7-29). The tumor cells often show marked nuclear pleomorphism and contain prominent eosinophilic cytoplasm (462). This tumor may resemble a malignant melanoma but unlike melanoma its cells are not immunoreactive for melanoma antigen HMB45, Melan-A, or S-100 protein, and it has immunohistochemical and electron microscopic features of typical squamous cell carcinoma.

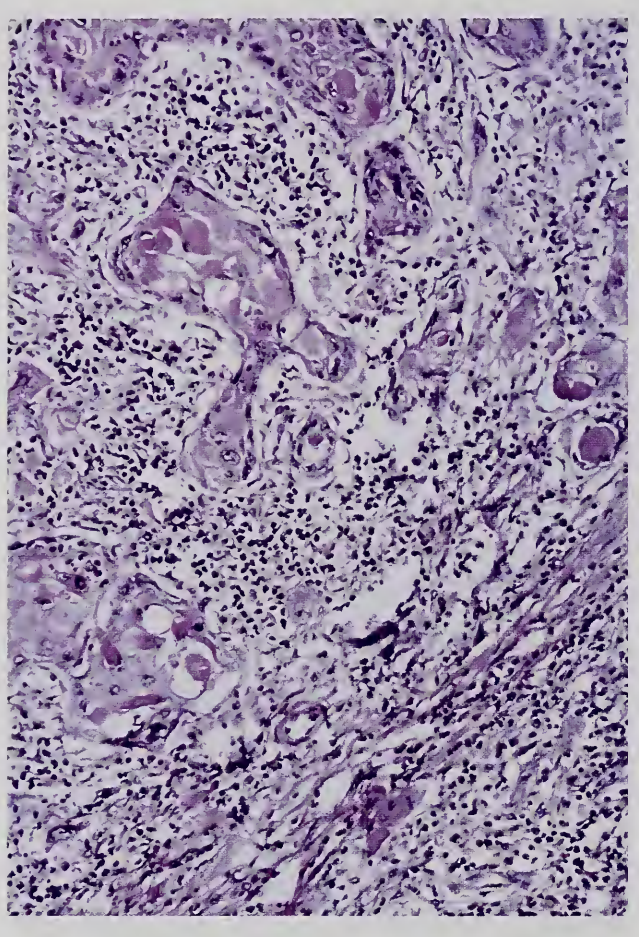


Figure 7-31

ADENOID (PSEUDOGLANDULAR) SQUAMOUS CELL CARCINOMA

Nuclear pleomorphism with acantholysis of tumor cells and gland-like formation in a poorly differentiated tumor with focal squamous differentiation. A moderate chronic inflammatory infiltrate is present in the dermis.

Spindle Cell Squamous Cell Carcinoma/ Squamous Cell Carcinoma with Sarcomatoid Features

Spindle cell squamous cell carcinoma is composed of elongated spindle-shaped cells that mimic a sarcoma (fig. 7-30). The stroma may also contain spindle-shaped cells, resulting in a sarcoma-like appearance (407). These tumors must be distinguished from mesenchymal spindle cell tumors, including leiomyosarcoma, malignant fibrous histiocytoma, and fibrosarcoma, as well as carcinosarcoma, spindle cell melanoma, and urothelial cell carcinoma with spindle cell features. The neoplastic epithelial spindle cells are immunoreactive for keratin, reflecting their epithelial origin (76,238,284). Spindle cell carcinoma with sarcomatoid features may contain tumor giant cells, which are immunoreactive for keratin (376).

Adenoid Squamous Cell Carcinoma

Adenoid squamous cell carcinoma is a morphologic variant of squamous cell carcinoma that is characterized by areas of pseudoglandular formation, related to cellular acantholysis (224). The gland-like spaces are lined by a single layer of squamous cells, and the lumens may contain dyskeratotic and acantholytic cells (fig. 7-31). This tumor variant may be mixed with squamous carcinoma of the usual type (190). Mucin (sialomucin) is characteristically not present; glycogen is present in the acantholytic cells. Histochemical findings support a high hyaluronic acid content in the basophilic material in the pseudoglandular spaces (190). The prognosis and frequency of regional lymph node involvement are similar to those of squamous cell carcinoma of the usual type.

Lymphoepithelioma-Like Carcinoma

Lymphoepithelioma-like carcinoma is a rare variant of squamous cell carcinoma that is usually observed in older women (57,397a). The tumor is composed of clusters or syncytial groups of neoplastic epithelial cells intermixed and surrounded by a lymphocytic infiltrate (fig. 7-32). The neoplastic epithelial cells are immunoreactive for high molecular weight cytokeratins, which distinguish them from inflammatory changes and lymphomas (fig. 7-32). Unlike lymphomas, including Ki-1 lymphomas, these epithelial cells are not immunoreactive for lymphocytic markers and do not have the molecular markers of lymphomas. Therapy for lymphoepithelioma-like carcinoma is wide local excision (partial deep vulvectomy). Additional therapy may be needed based on the stage of the tumor (57).

Verrucous Carcinoma

Definition. *Verrucous carcinoma* is a highly differentiated squamous cell carcinoma that has a verrucous pattern of growth and invades with a pushing border in the form of bulbous pegs of neoplastic cells (38). The term *giant condyloma of Buschke-Lowenstein* is considered

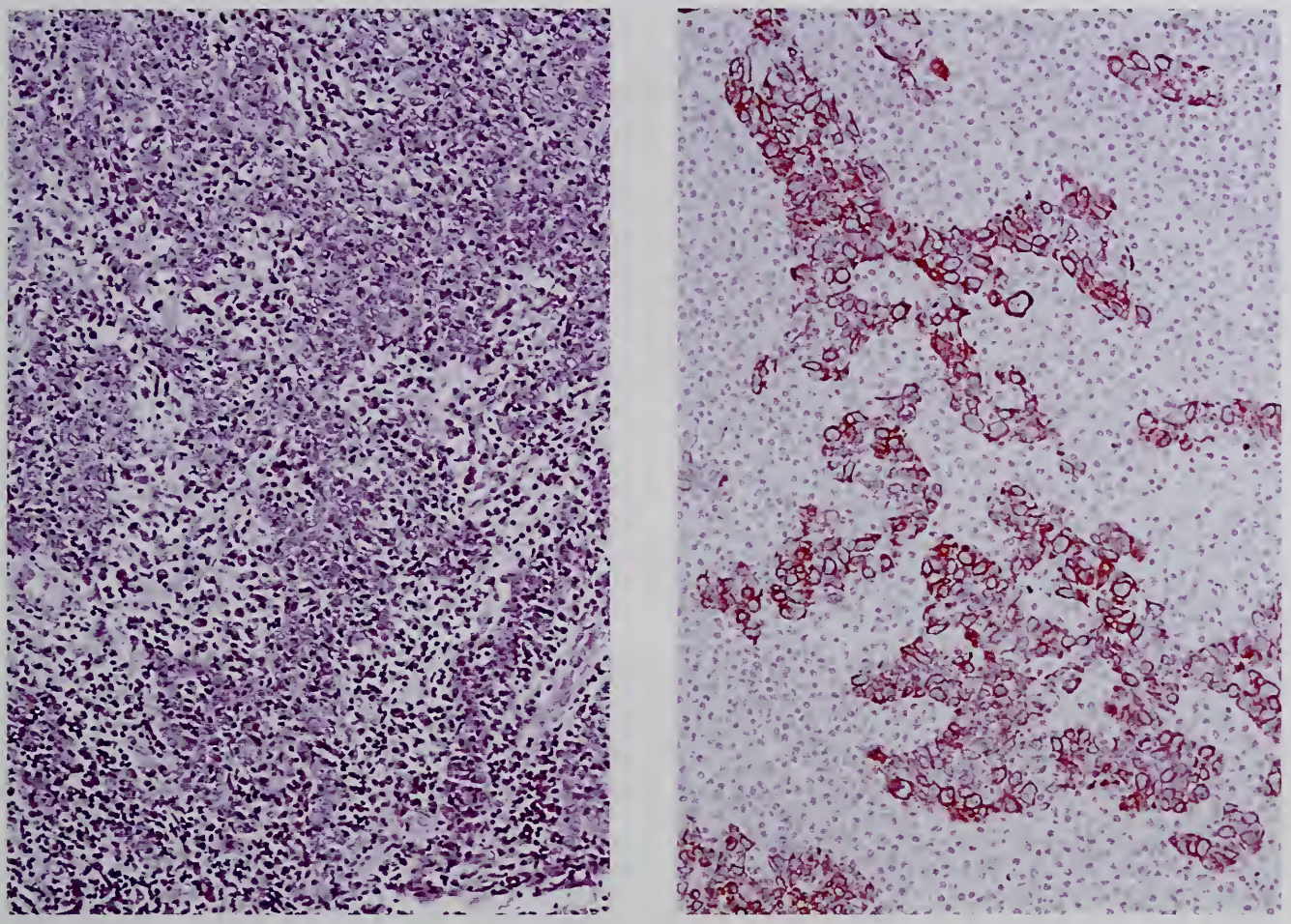


Figure 7-32

LYMPHOEPITHELIAL CARCINOMA

Left: The neoplastic squamous cells in groups are surrounded by a dense chronic inflammatory infiltrate consisting predominately of lymphocytes.

Right: The invasive squamous cells are immunoreactive with high molecular weight keratin.

to be a synonym for verrucous carcinoma but its use is not recommended. Squamous cell carcinomas having some of the architectural features of verrucous carcinoma but lacking a high degree of differentiation should not be designated verrucous carcinoma (209).

Clinical Features. Verrucous carcinoma is a papillary exophytic growth that may distort or completely obscure the vulva. Secondary infection may be associated with a malodorous discharge. Regional lymph nodes are usually not enlarged.

Gross Findings. The tumor has a papillomatous granular appearance, and may be markedly hyperkeratotic.

Microscopic Findings. The microscopic features of verrucous carcinoma include prominent acanthosis with a pushing tumor-dermal interface and bland cytologic features (fig. 7-33). Large bulbous nests of squamous epithelial cells characterize the deep advancing margin. There is minimal nuclear pleomorphism, with the greatest degree of nuclear atypia nearest the dermal interface. The nuclei may have coarse chromatin and variable-sized nucleoli, distinguishing them from normal adjacent keratinocytes. Mitotic figures are rare, and when present, are normal. The abundant cytoplasm of the tumor cells is eosinophilic, without dyskeratosis. Koilocytosis is not a feature of this tumor. Parakeratosis and/or hyperkeratosis is usually present, and may be prominent. There is an absence of fibrovascular cores separating the bulbous epithelial downgrowths. An inflammatory infiltrate within the dermis is usually present.

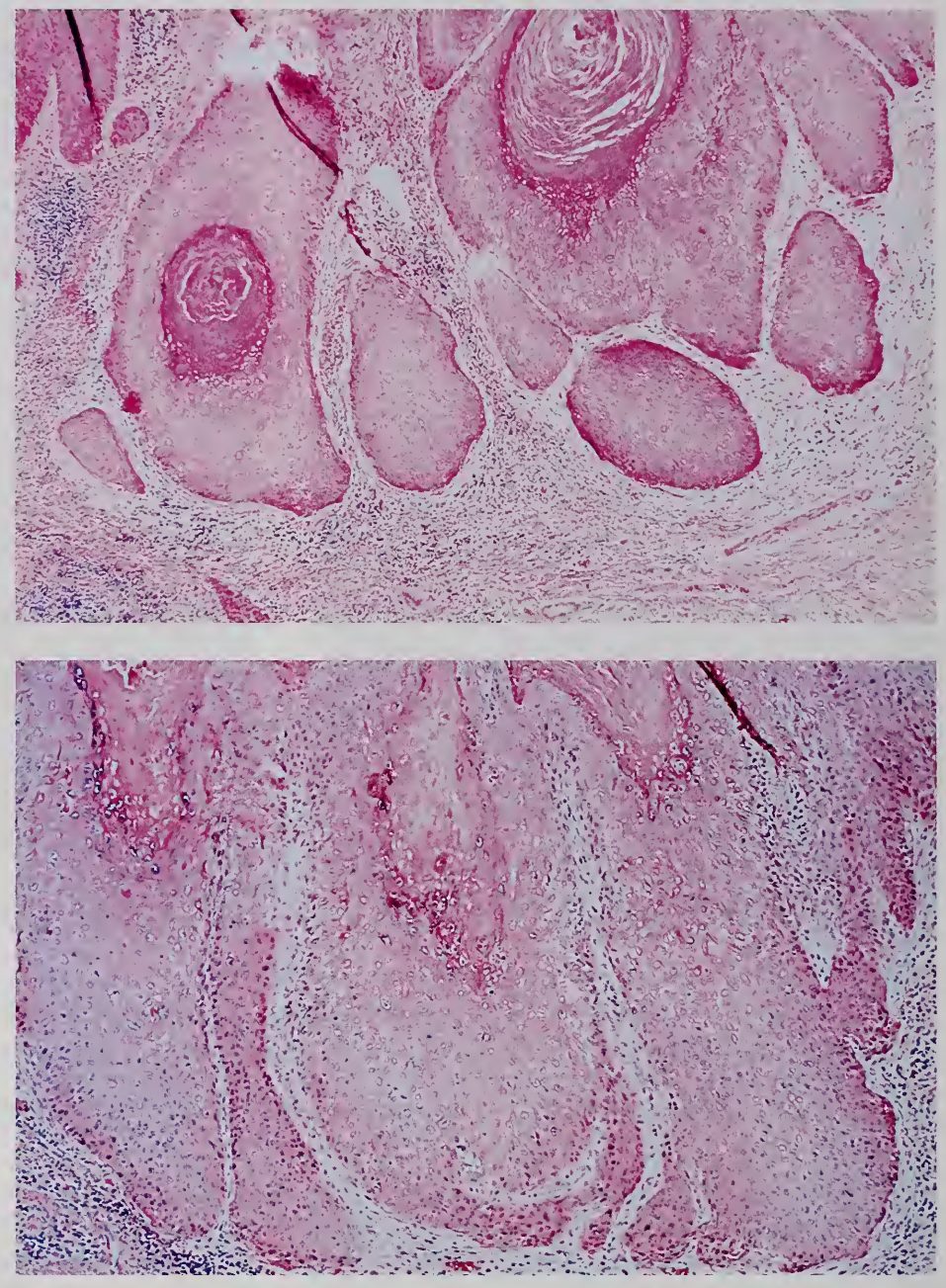


Figure 7-33

VERRUCOUS CARCINOMA

Top: The tumor has prominent acanthosis, expands the epithelial rete ridges, and compresses the intervening dermal papillae. The tumor-dermal interface is of a pushing type. The tumor is composed of mature-appearing squamous epithelial cells with little or no cellular atypia. The dermis is not fibrotic and the inflammatory response is minimal.

Bottom: The tumor expands and elongates the epithelial rete ridges and is composed of mature-appearing squamous epithelial cells with little or no cellular atypia. The tumor-dermal interface is of a pushing type, and no tumor cells are present within the dermis. There is little or no cellular atypia. A mild chronic inflammatory infiltrate is in the dermis.

Epithelial changes have been reported adjacent to verrucous carcinoma, including marked acanthosis with verruciform features, loss of the granular layer with "multilayered" parakeratosis and many parakeratotic cells, and superficial epithelial pallor. These changes have been termed *vulvar acanthosis with altered differentiation (VAAD)* and were reported adjacent to 7 of 9 verrucous carcinomas (288). In this study, lichen simplex chronicus was also found in 7 cases, and lichen sclerosus in 1 case. Verrucous carcinoma has been reported to be associated with HPV, typically type 6, or variants of type 6 (311,347,427). These tumors are typically diploid. Condyloma acuminatum and squamous cell carcinoma may be adjacent to verrucous carcinomas (96,98).

Differential Diagnosis. The differential diagnosis includes exophytic squamous cell carcinoma of the usual type, warty carcinoma, and condyloma acuminatum. Squamous cell carcinoma of the usual type has greater nuclear pleomorphism and a more irregular type of dermal infiltration than the bulbous rete pegs of verrucous carcinoma. Warty carcinoma, despite its verruciform appearance, has fibrovascular cores within the papillary fronds, unlike

verrucous carcinoma. In addition, these tumors display greater nuclear atypia, koilocytosis, and, at their deep margin, invade like typical squamous cell carcinomas. Condyloma acuminatum is characterized by a complex branching papillary architecture with vascular papillae, lacks bulbous downgrowths, and typically shows koilocytosis.

Treatment and Prognosis. Verrucous carcinomas may recur locally after excision. Lymph node metastasis is rare, and its presence should prompt reevaluation of the lesion for areas of usual type squamous cell carcinoma. Wide local excision (partial deep vulvectomy) without lymph node dissection is the most common method of therapy. If the tumor is completely excised, the prognosis is excellent (9).

Basal Cell Carcinoma

Definition. *Basal cell carcinoma* is a locally infiltrative tumor arising in the epidermis or hair follicles. Within the infiltrating nests of tumor the peripheral cells simulate the basal cells of the epidermis and are typically palisaded along the margins.

General Features. Basal cell carcinomas of the vulva account for only 5 to 7 percent of vulvar carcinomas (84,109). They occur primarily in elderly white women (mean age, 70 to 76 years). Symptoms include pruritus, irritation, soreness, and bleeding. These tumors present as a mass, ulcer, pigmented lesion, or depigmented lesion (25,35,394). Most occur on the labia majora. Basal cell carcinoma of the vulva has been reported to occur concurrently with vulvar Paget disease (184). Basal cell carcinomas are not associated with HPV.

Gross Findings. The tumor is usually firm, well circumscribed, granular, and raised or ulcerated. Most basal cell carcinomas of the vulva are 2 cm or less in diameter, but may be larger (25).

Microscopic Findings. Like basal cell carcinomas elsewhere on the skin, the tumor can have a variety of growth patterns: most are plaque-like or nodular. The tumor typically has an ulcerated or eroded surface and clefting at the dermal-epidermal interface (353). Approximately half of the cases are of infiltrative type. Characteristically, the tumor cells are small with hyperchromatic, elongated nuclei, although some pleomorphism may be seen (fig. 7-34). The cells may be grouped in trabecular or club-shaped masses, with the peripheral cells arranged in a palisaded fashion. Squamous differentiation, characterized by enlarged cells with abundant eosinophilic cytoplasm, sometimes demonstrating intercellular bridges, may be found within the nests of what is otherwise a typical basal cell carcinoma. Such tumors are still considered basal cell carcinomas. Nests of tumor cells may be surrounded by a hyalinized reactive dermis.

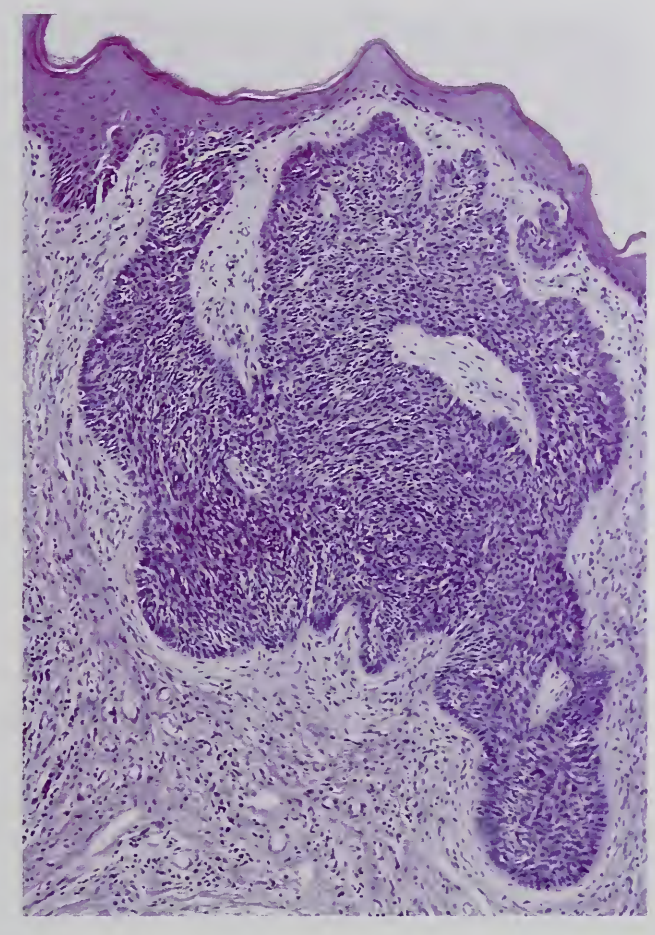


Figure 7-34

BASAL CELL CARCINOMA

This tumor is composed of small uniform cells with peripheral palisading of nuclei. The tumor has a pushing type interface with the dermis. The surface epithelium is focally involved but is otherwise unremarkable. There is a mild chronic inflammatory cell infiltrate in the adjacent dermis.

Immunohistochemistry. Basal cell carcinomas express BerEP4, which is not expressed by the usual squamous cell carcinoma (416).

Differential Diagnosis. Basal cell carcinoma may resemble basaloid VIN, basaloid

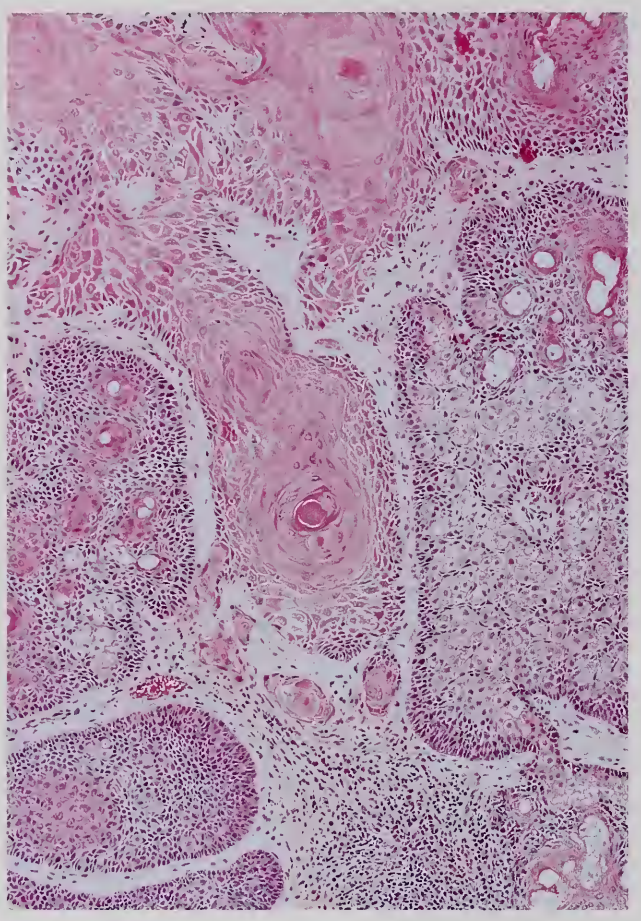


Figure 7-35

SEBACEOUS CARCINOMA

The tumor has features of basal cell and squamous cell carcinomas, with focal areas of vacuolated sebaceous cells.

squamous cell carcinoma, or trichogenic skin appendage tumors. Basal cell carcinoma typically lacks the nuclear pleomorphism of VIN or basaloid squamous cell carcinoma and unlike VIN or squamous cell carcinoma expresses BerEP4. Various trichogenic tumors including trichoepithelioma, trichoblastoma, trichodiscoma, trichomyxoma, and trichofibroma may resemble basal cell carcinoma (353). These trichogenic tumors are composed of follicular germinative cells and typically do not have surface ulceration or clefting at the dermal-epidermal interface, as seen with basal cell carcinoma, nor do they have the infiltrative pattern of invasion seen with invasive basal cell carcinoma. In addition, trichogenic tumors usually have other patterns of differentiation, including apocrine, sebaceous, trichogenic, and keratinization, which are typically not seen in basal cell carcinoma (353).

Treatment and Prognosis. Approximately half of the basal cell carcinomas of the vulva are locally infiltrative. Primary treatment is local excision (partial deep vulvectomy) (25). Local recurrence is reported in 9 to 20 percent of cases (25,109). Metastasis to regional lymph nodes is rare (25,109). The overall prognosis of patients with these tumors is excellent, with only a rare death reported (25).

Adenoid Basal Cell Carcinoma

Adenoid basal cell carcinoma is a variant of basal cell carcinoma with focal tubular and gland-like differentiation (268,282).

Metatypical Basal Cell Carcinoma

Metatypical basal cell carcinoma (basosquamous carcinoma) consists of both basal cell carcinoma and squamous cell carcinoma (35). It occurs at a mucocutaneous junction and is composed of small, uniform, hyperchromatic epithelial cells with a growth pattern typical of basal cell carcinoma. Adjacent to the basal cell component, cells demonstrate more prominent eosinophilic cytoplasm, nuclear enlargement, and pleomorphism, features characteristic of squamous cell carcinoma.

Sebaceous Carcinoma

Sebaceous carcinoma is a tumor with sebaceous differentiation that otherwise has features of metatypical basal cell carcinoma. This tumor has been reported in association with VIN (187). Thomsen-Friedenreich (T) antigen is usually expressed in the cytoplasm of the basaloid and intermediate cells of sebaceous carcinoma (fig. 7-35) (171).

The differential diagnosis of sebaceous carcinoma includes basaloid squamous cell carcinoma, Merkel cell tumor, and metastatic small cell carcinoma. Basaloid squamous cell carcinomas are composed of neoplastic squamous cells with nuclear pleomorphism and coarse nuclear chromatin. Some dyskeratosis may be present. The peripheral palisading so characteristic of sebaceous cell carcinoma is not present in basaloid squamous cell carcinoma. The epithelium adjacent to basaloid squamous cell carcinoma may also have basaloid or warty VIN. The nuclei

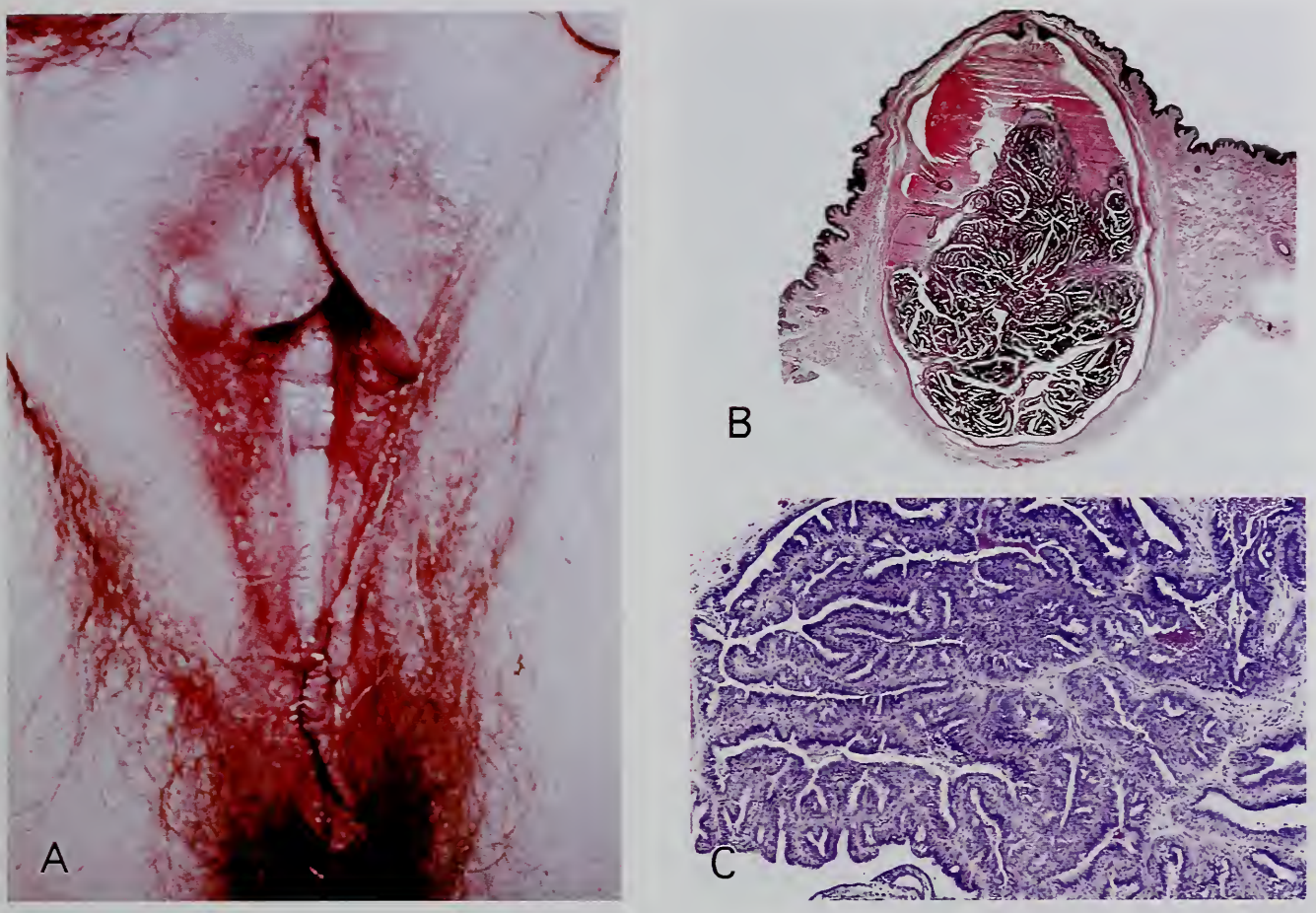


Figure 7-36

PAPILLARY HIDRADENOMA

A: The tumor is typically within the interlabial sulcus. In this case, the epithelial surface is intact and the lesion well circumscribed, resembling a cyst.

B: The tumor has a complex glandular pattern without infiltration of the dermis.

C: The glands are of variable size and well differentiated, with a secretory epithelial lining and an underlying myoepithelial layer.

of Merkel cell tumors have stippled chromatin. These tumors, as well as metastatic small cell carcinomas, have a more diffusely infiltrative pattern. Their cells are somewhat smaller with more hyperchromatic nuclei than basal cell carcinoma. They are immunoreactive for neuroendocrine markers and have a distinctive perinuclear, dot-like immunoreactive cytoplasmic staining pattern with cytokeratin markers.

Basal Cell Carcinoma Mixed with Squamous Cell Carcinoma (Mixed Carcinoma)

Basal cell carcinoma may be *mixed with squamous cell carcinoma*. Unlike basal cell carcinomas, such mixed carcinomas can be locally aggressive and metastasize, similar to squamous cell carcinoma.

BENIGN GLANDULAR LESIONS

Papillary Hidradenoma (Hidradenoma Papilliferum)

Definition. *Papillary hidradenoma (hidradenoma papilliferum)* is a benign tumor of apocrine sweat gland origin, composed of epithelial cells lining complex, delicate fibrovascular branching stalks. The tumor cells include both secretory and myoepithelial cells and have as their origin the specialized apocrine-like anogenital glands within the intralabial sulcus (432,433).

General Features. This uncommon tumor is seen predominantly in white women, and presents after puberty, when apocrine gland development occurs. The tumor is characteristically solitary. It is located in, or immediately

adjacent to, the intralabial sulcus and ranges in location from the lateral aspects of the labia minora to the lateral aspects of the labia majora (fig. 7-36A). Hidradenoma usually presents as an asymptomatic mass but may cause pruritus, ulceration, bleeding, and watery exudates.

Gross Findings. The tumor characteristically is a well-circumscribed subcutaneous nodule measuring 0.5 to 1.0 cm.

Microscopic Findings. The well-circumscribed tumor compresses the adjacent stroma and forms pseudocapsules. It is composed of complex tubules and acini lined by tall columnar cells that may have an apocrine appearance, with underlying myoepithelial cells (fig. 7-36B). The spaces contain PAS-positive diastase-resistant secretions (267). Mild nuclear pleomorphism and minimal mitotic activity may be seen. Electron microscopy confirms the apocrine nature of the cells, which contain secretory granules and lamellar bodies and show evidence of decapitation secretion (170). The tumor cells are CEA negative, supporting their specialized apocrine glandular origin, unlike tumors of eccrine sweat gland origin, which contain CEA (285). An intraductal carcinoma of mammary type arising in a papillary hidradenoma of the vulva has been reported (324).

Differential Diagnosis. The differential diagnosis includes skin appendage adenocarcinoma (455), metastatic carcinomas, and endometriosis. Adnexal adenocarcinomas do not have a cystic or papillary configuration and lack a myoepithelial layer. In addition, these tumors are more cellular and display more nuclear atypia. Metastatic carcinomas lack a two-cell layer, are infiltrating, and usually have features consistent with their site of origin. Endometriosis contains endometrioid glands and stroma, and the epithelial cells are secretory and ciliated. Papillary hidradenoma may be microscopically indistinguishable from intraductal papilloma arising in mammary-like tissue within the vulva.

Treatment and Prognosis. Papillary hidradenoma is a benign tumor that is treated by excisional biopsy.

Nodular (Clear Cell) Hidradenoma

Definition. *Nodular (clear cell) hidradenoma* is a benign tumor of eccrine sweat gland origin composed of distinctive small cells with clear cytoplasm. Other terms for this tumor include *clear cell myoepithelioma, clear cell nodular hidradenoma, solid-cystic hidradenoma, eccrine acrospiroma,* and *eccrine sweat gland adenoma of clear cell type.*

General Features. Nodular hidradenoma is rare on the vulva. The tumor forms solitary subcutaneous nodules. Patients may present with pruritus or a burning sensation, but usually are asymptomatic. The tumor may be tender on palpation. It is believed to arise from the epithelial matrices of eccrine sweat gland primordia.

Gross Findings. The tumor is usually 0.5 to 2.0 cm in diameter, solid, and well circumscribed. On section, it is tan to gray and predominantly solid; cystic or hemorrhagic areas may be present.

Microscopic Findings. Nodular hidradenoma is well circumscribed. It is composed of uniform polygonal cells with small round to irregularly shaped nuclei and prominent clear cytoplasm (fig. 7-37). The cells are typically arranged in lobules separated by delicate strands of connective tissue that are rich in collagen. Cystic spaces may be seen within the lobules and tubules may form. Mitotic activity is rare. The surface epithelium is usually unremarkable, but may be acanthotic or thin, sometimes accompanied by ulceration. The histochemical and ultrastructural features of the tumor confirm its eccrine sweat gland origin.

Differential Diagnosis. The differential diagnosis includes metastatic clear cell adenocarcinoma, metastatic renal cell carcinoma, clear cell leiomyoma, clear cell carcinoma arising primarily within the skin, including tumors of hair shaft, and clear cell variants of squamous cell carcinoma. Also included in the differential diagnosis are related benign skin appendage tumors. Clear cell and renal cell carcinomas are infiltrative and have minimal to marked nuclear pleomorphism. They are often multiple, involve both deep and superficial tissues, and may have vascular space involvement. Clear cell leiomyoma has the immunohistochemical features of smooth muscle. Clear cell carcinomas of skin or hair shaft are infiltrative tumors that have nuclear pleomorphism and hyperchromasia. Examination of the adjacent tissues may help to identify their origin. Eccrine acrospiroma and other squamous poroadenomas are morphologically distinctive and are described in other sources.

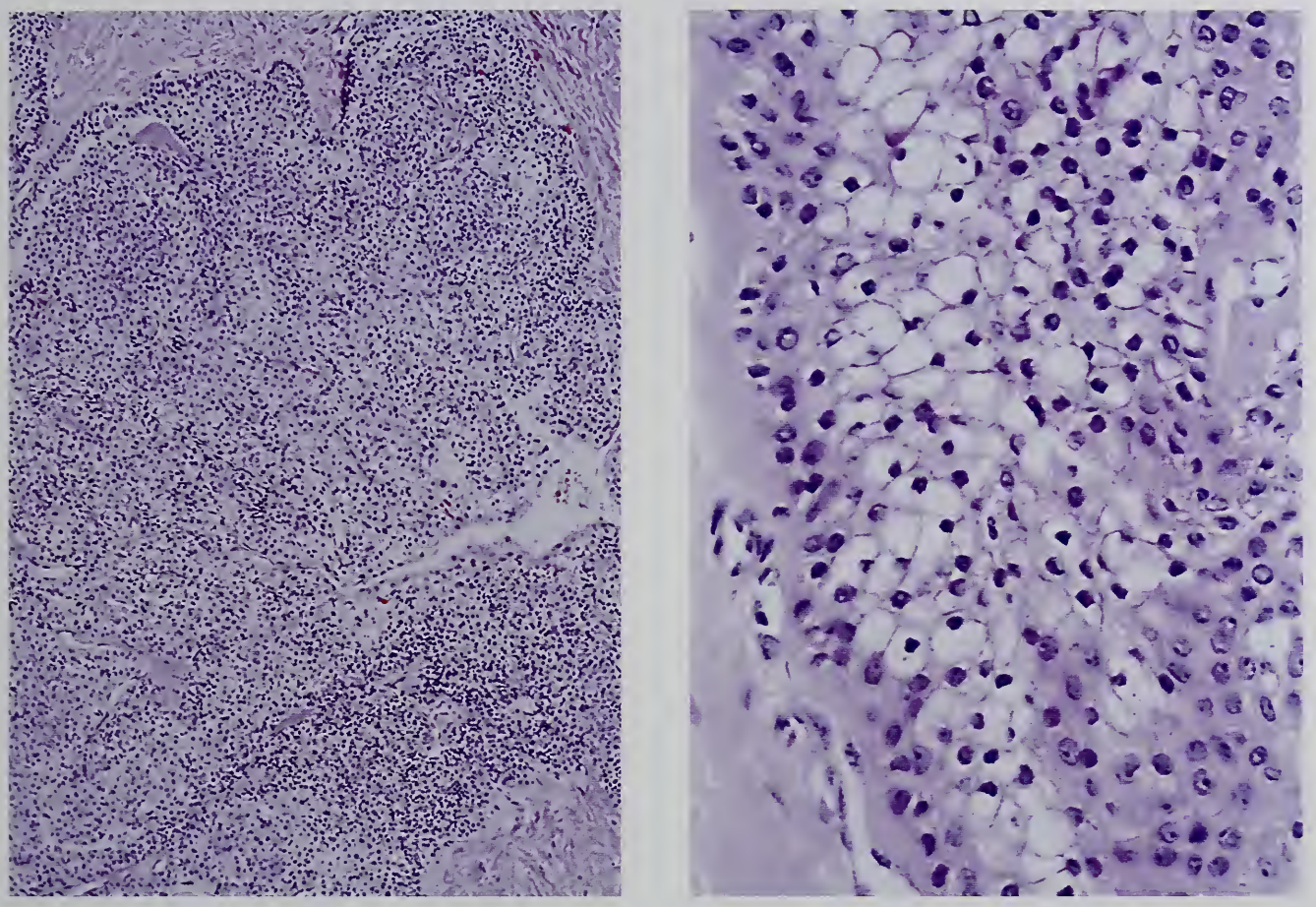


Figure 7-37

NODULAR (CLEAR CELL) HIDRADENOMA

Left: The tumor is well demarcated and has complex, solid to papillary architecture.
Right: The cells are uniform and polygonal, with small, round nuclei. Some cells have prominent clear cytoplasm.

Treatment and Prognosis. Clear cell hidradenoma is a benign tumor that is treated by excisional biopsy.

Syringoma

Definition. *Syringoma* is a benign tumor of eccrine duct origin characterized by multiple small and generally uniform epithelial-lined tubules and cysts within a fibrous stroma. It is considered an adenoma of eccrine duct origin.

General Features. Syringoma is an uncommon vulvar tumor that typically occurs in young women. The youngest reported patient was a 9-year-old girl (45). It is rare in postmenopausal women (135). Patients may present with pruritus although they are more commonly asymptomatic. The tumors are usually multiple, clustered, and bilateral. Symmetric papules occur most commonly on the labia majora and less commonly on the lateral aspects of the labia minora. Papules may also occur on the inner thighs (183,479).

Gross Findings. These tumors are typically small, ranging from 1 to 3 mm in diameter, firm, and flesh colored.

Microscopic Findings. Syringomas lie within the dermis and are well circumscribed with pushing borders. They are composed of multiple duct-like structures, some of which may be dilated or cystic, and many of which have a distinctive comma shape (fig. 7-38). Two layers of epithelial cells can be seen. Part of the cyst epithelium may be flattened. Within the cysts, the secretory material is PAS positive and diastase resistant. Rupture of cysts may be associated with a chronic inflammatory foreign body reaction

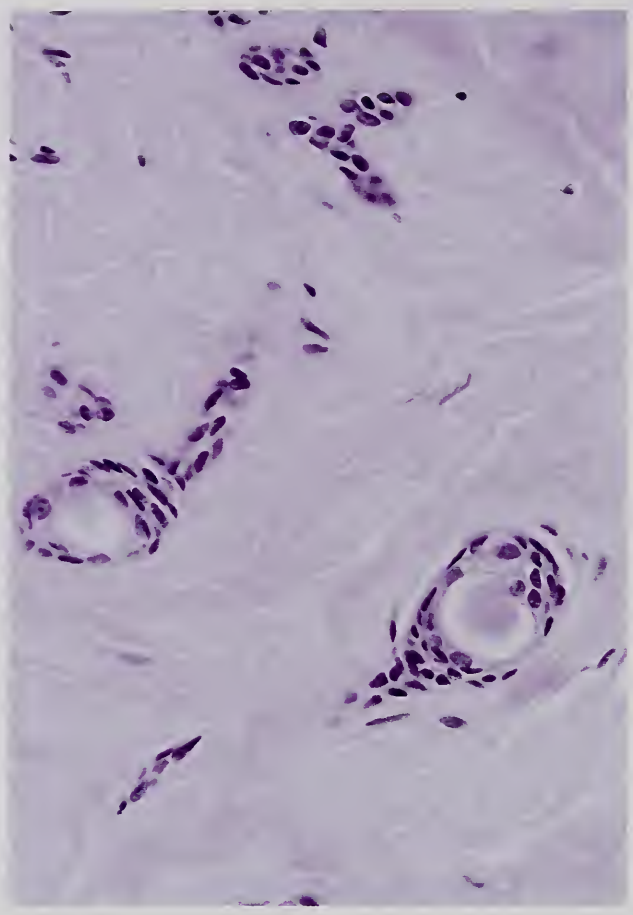


Figure 7-38

SYRINGOMA

The tumor, within the superficial dermis, contains clusters of small ducts, some of which are comma-shaped. Some of the ducts have two cell layers. The adjacent dermis is fibrous.

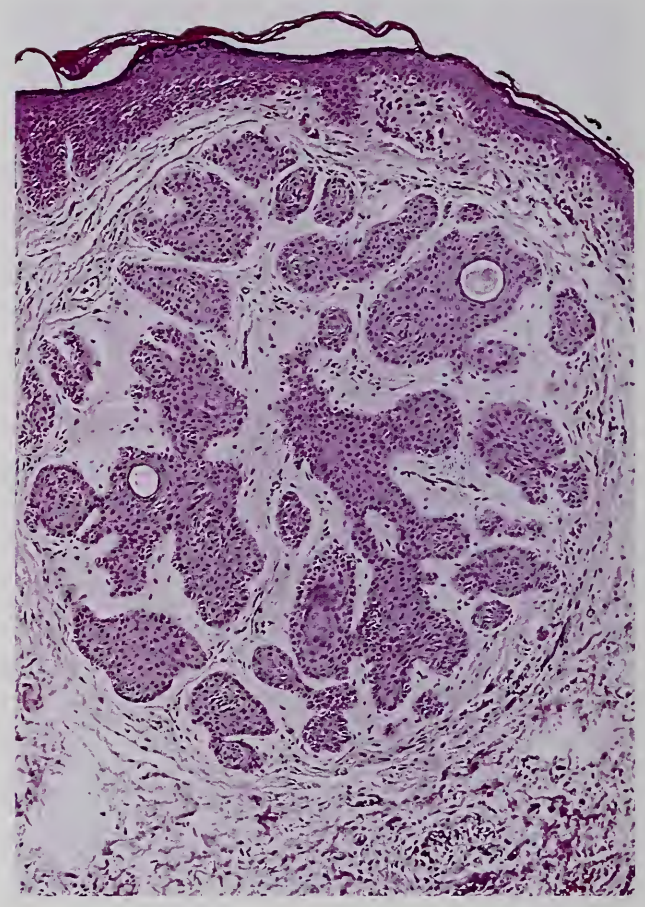


Figure 7-39

TRICHOEPITHELIOMA

This small vulvar tumor is entirely within the superficial fibrous dermis. Small epithelial cell nests with radiating buds are present. Some cells groups have cystic centers.

and subsequent calcification. A superficial inflammatory reaction may also be seen (135,418). The surrounding stroma is fibrous. Syringomas have the characteristic features of intraepidermal eccrine glands by both immunohistochemical and electron microscopic studies. Syringomatous differentiation has been described within mixed skin appendage tumors with chondroid stroma, giving rise to the term *chondroid syringoma*.

Differential Diagnosis. The differential diagnosis includes metastatic and primary adenocarcinomas. Adenocarcinomas are infiltrative, have nuclear pleomorphism, form glands of variable sizes and shapes, and may involve the deep and the superficial dermis. Sweat gland carcinomas may have solid and differentiated areas, but lack the nuclear and structural uniformity of syringoma.

Treatment and Prognosis. Patients are usually asymptomatic and treatment is seldom necessary. Surgical excision or other ablative techniques can be used in symptomatic cases.

Mixed Tumor of the Vulva (Pleomorphic Adenoma, Chondroid Syringoma)

Mixed tumor of the vulva is a rare neoplasm that presents as a solid, subcutaneous tumor involving the labia majora and/or the Bartholin gland area. Histopathologic findings are similar to those of mixed tumors of the parotid and other salivary glands. The tumor is composed of epithelial-lined tubules or nests, occasionally with benign squamous differentiation, admixed with a fibrous stroma which may include chondromatous, osseous, and myxoid elements. These stromal-related elements are believed to

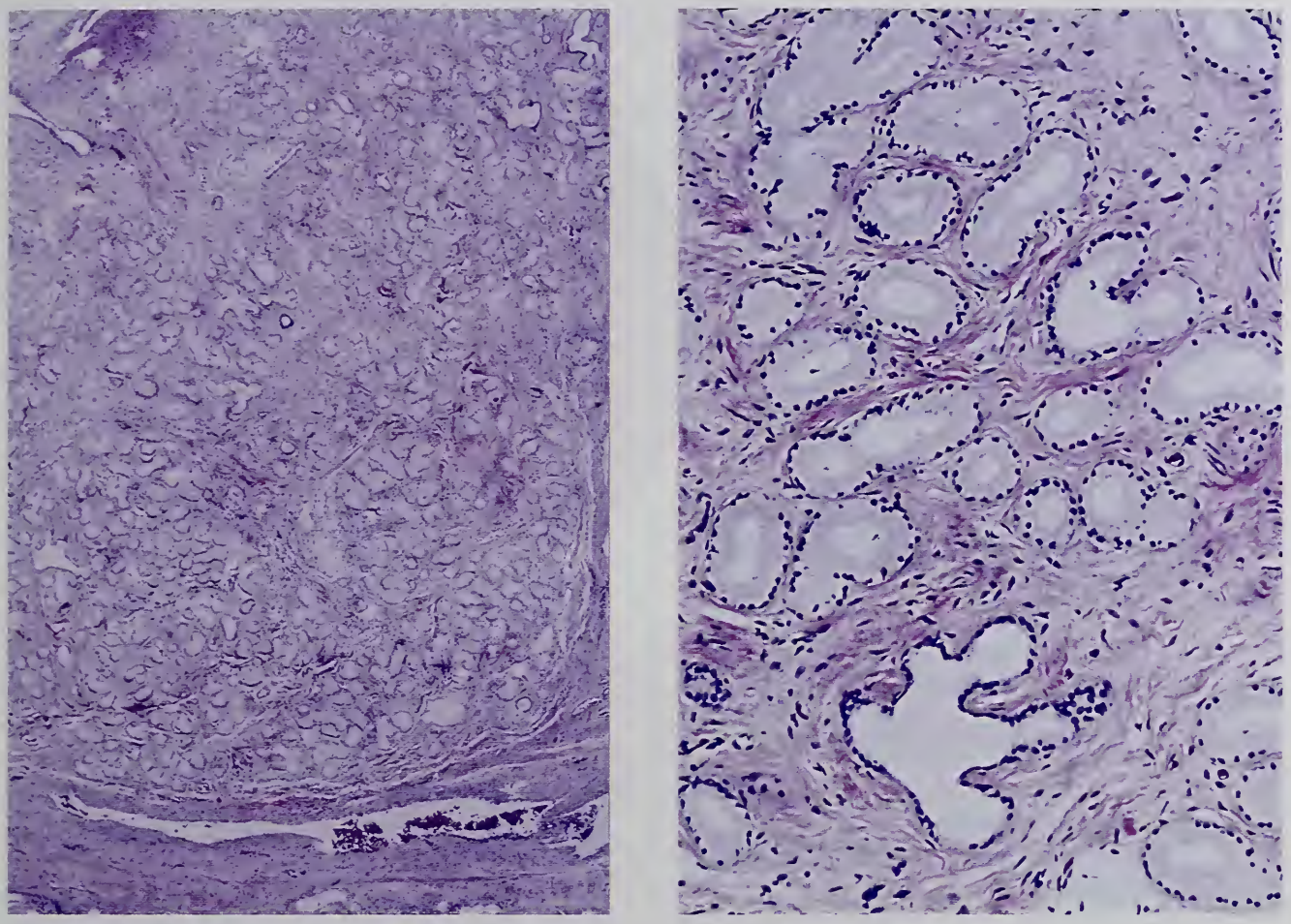


Figure 7-40

ADENOMA OF MINOR VESTIBULAR GLANDS

Left: The well-circumscribed tumor is contiguous with clustered glands with mucin-producing glandular epithelial cells.

Right: Small clustered glands are present without cellular atypia.

arise from pluripotential myoepithelial cells that, in the vulva, are found in the Bartholin glands, sweat glands, and specialized anogenital glands. Mixed tumor of the vulva is benign but may recur locally. Adenocarcinoma, however, arising in a patient with vulvar chondroid syringoma has been reported (130).

Trichoepithelioma

The benign hair follicle tumor, *trichoepithelioma*, is rare on the vulva (68). It presents as single or multiple, firm, nonulcerated nodules. On microscopic examination, the tumor is composed of nests of basaloid cells with small cysts containing keratin ("horn cysts"), surrounded by stroma. The basal cells are monomorphic and lack nuclear hyperchromasia or atypia, although they may resemble basal cell carcinoma cells (fig. 7-39). In contrast to basal cell carcinoma and basaloid carcinoma, trichoepithelioma is not infiltrative. It has horn cysts and may exhibit giant cells with granulomas related to the rupture of the horn cysts. There may be hair-forming elements (although true hair or hair buds are rarely seen), but no intraepithelial neoplastic component, as seen in basal cell or basaloid squamous cell carcinoma.

Proliferating Trichilemmal Tumor (Trichilemmoma)

Proliferating trichilemmal tumor (trichilemmoma) is a rare, slow-growing, benign tumor of the vulva that occurs in the dermis of the labia majora (14). The tumor has a lobulated appearance microscopically, with a pushing border

Table 7-4

CLASSIFICATION OF VULVAR PAGET DISEASE OF CUTANEOUS AND NONCUTANEOUS ORIGIN[a]

Paget disease of primary cutaneous origin (type 1)
Paget disease as a primary intraepithelial neoplasm
Paget disease as an intraepithelial neoplasm with invasion
Paget disease as a manifestation of an underlying adenocarcinoma of skin appendage or vulvar glands
Paget disease of noncutaneous origin
Paget disease secondary to anal-rectal adenocarcinoma (type 2)
Paget-like disease of urothelial origin (pagetoid urothelial intraepithelial neoplasia [PUIN] type 3)
PUIN as a manifestation of intraepithelial urothelial neoplasia (carcinoma in situ)
PUIN as a manifestation of urothelial carcinoma
Paget disease as a manifestation of other carcinomas (endocervix, endometrium, ovary, etc.)

[a]Data from reference 461.

and may show no connection with the overlying epithelium. The tumor cells are palisaded peripherally and have increased cytoplasm as they stratify toward the centers of nests that contain amorphous keratin. A granular layer is not identified. Nuclear pleomorphism and calcification may be present.

Trichilemmal cysts (proliferating trichilemmal cysts, pilar tumors) have also been described on the vulva (47,345), as has *trichoblastic fibroma* (139). Local excision is diagnostic and therapeutic.

Adenoma of Minor Vestibular Glands

Adenoma of the minor vestibular glands is a rare benign tumor found within the vulvar vestibule. It is usually 1 to 2 mm in diameter, although larger adenomas have been observed. This tumor is composed of nodular clusters of small mucin-secreting glands lined with mucin-secreting columnar epithelium (fig. 7-40) (15,118). The lesion may be nodular hyperplasia and not a true neoplasm. In the majority of the reported cases, the lesion is detected as an incidental finding within a partial or total vulvar vestibulectomy specimen excised in the course of treatment for vulvar vestibulitis (123).

INTRAEPITHELIAL NEOPLASMS: PAGET DISEASE AND PAGET-LIKE LESIONS

Although traditionally considered a single disease process, vulvar *Paget disease* represents several distinct entities, as summarized in Table 7-4 (461).

Primary Cutaneous (Intraepithelial) Paget Disease (Type 1 Paget Disease)

Definition. *Primary cutaneous Paget disease* is an intraepithelial neoplasm characterized by a proliferation of neoplastic glandular type cells that primarily arise within the epithelium. It may arise as an underlying adenocarcinoma of skin appendages.

General Features. Vulvar Paget disease accounts for approximately 2 percent of all vulvar neoplasms. It typically occurs in white postmenopausal women (19,148), but has been described in a 24-year-old black woman (406).

Gross Findings. The disease typically presents as a symptomatic, red eczematoid lesion that clinically may resemble a dermatosis (468). Within the red lesion, small foci of white hyperkeratotic or edematous epithelium may be seen (fig. 7-41). It also presents as an erythematous lesion. The lesion may be localized, often involving the lateral aspects of the labium majus, but may be extensive and involve most or all of the vulva, as well as perianal areas and the upper inner thighs. The lesion usually has irregular margins and a moist, weeping surface.

Microscopic Findings. Paget disease of cutaneous origin is usually an entirely intraepithelial neoplasm, but can spread within the epithelium and involve the adjacent apocrine and/or eccrine glands. Intraepithelial Paget cells can also invade the dermis, a pattern observed in less than 10 percent of the cases (167, 227,337,473).

The Paget cells within the epithelium occur singly and in groups (fig. 7-41). Occasionally, gland-like acinar spaces are formed within cell groups. The cells may involve skin appendages and the surface epithelium. Typically, they are grouped predominantly within the basal and parabasal zones, with fewer cells present superficially. The cells are generally larger than the adjacent keratinocytes and have finely granular amphophilic to basophilic cytoplasm. The cytoplasm is paler than that of adjacent keratinocytes and may be vacuolated and form signet ring cells. The Paget cell nucleus is typically round or oval, and as large or larger than that of the adjacent keratinocytes, with one or more prominent nucleoli. Nuclear

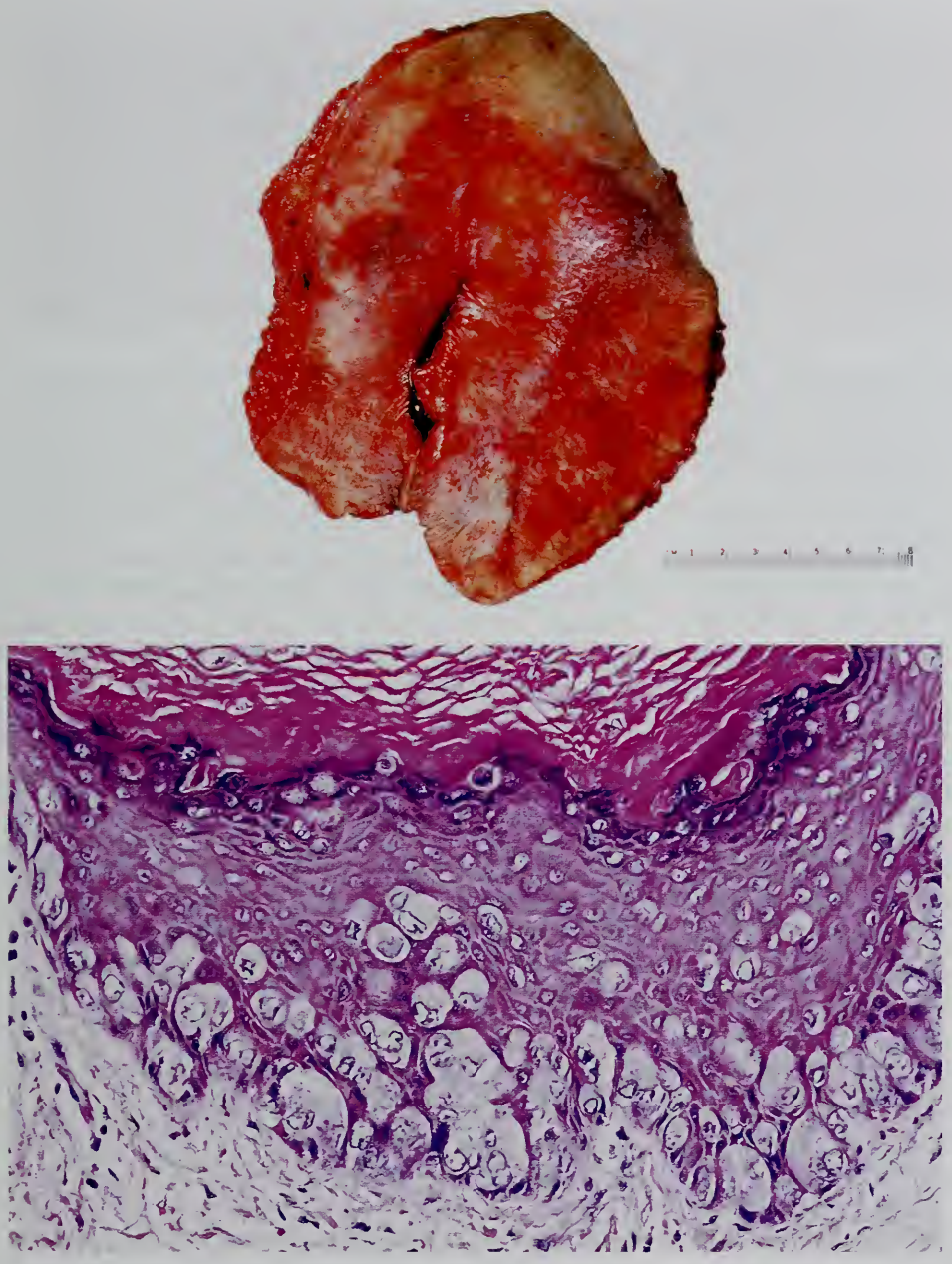


Figure 7-41

PAGET DISEASE, CUTANEOUS TYPE

Top: Total vulvectomy specimen is eczematoid, with islands of white epithelium. It involves a large area of the right labia majus and a smaller area in the upper left labia majus. (Courtesy of Dr. Bridgett Ronnett, Baltimore, MD.)

Bottom: The large pale Paget cells are single and in groups within the epithelium. They involve most of the epithelium but are primarily within the basal and parabasal areas; a few isolated cells are more superficial. Unlike the keratinocytes, these cells have abundant clear cytoplasm. The nuclei are generally large and have paler nuclear chromatin and more prominent nuclei than the nuclei of the adjacent keratinocytes.

chromatin varies from vesicular and finely granular to coarsely hyperchromatic. Mitotic figures may be found but are not frequent.

Paget cells are identified by cytologic examination of scrapings from saline-moistened areas (289). Paget disease of cutaneous origin may be locally invasive, or found overlying a skin appendage or Bartholin gland adenocarcinoma. Underlying associated adenocarcinoma, or invasive Paget disease, occurs in approximately 10 to 20 percent of women with vulvar Paget disease.

Paget disease can be associated with a variety of benign proliferative epithelial lesions, as observed in 32 percent of vulvar Paget disease and 92 percent of perianal Paget disease. These proliferative lesions include fibroepithelioma-like hyperplasia, squamous cell hyperplasia, and papillomatous hyperplasia (34). Vulvar squamous neoplastic changes were associated with vulvar Paget disease in 2 of the 22 cases (34), with 1 case of VIN and 1 invasive squamous cell carcinoma; no such lesions were observed in patients with perianal Paget disease.

Table 7-5

IMMUNOHISTOCHEMICAL FINDINGS IN VULVAR PAGET DISEASE OF CUTANEOUS AND NONCUTANEOUS TYPES[a]

	CK7[b]	UPK	CK20	GCDFP-15	CEA
As a primary skin neoplasm	+	–	–	+	+
Paget-like neoplasm related to urothelial carcinoma	+	+	(+)	–	–
Related to anorectal carcinoma	–	–	+	–	+

[a]Data from references 44, 302, and 461.
[b]CK = cytokeratin; UPK = uroplakin III; GCDFP-15 = gross cystic disease fluid protein 15; CEA = carcinoembryonic antigen.

Immunohistochemical Findings. The cytoplasm of Paget cells of cutaneous origin contains neutral and acid mucopolysaccharides, as reflected in staining with mucicarmine, PAS, aldehyde fuchsin, and Alcian blue. The mucin stains may be positive in only a small number of cells, and may therefore not be identified in small biopsy specimens. Paget cells occasionally contain intracytoplasmic melanin; consequently, a melanin stain is not useful for differentiating Paget disease from melanoma. The histochemical findings described above, as well as the presence of CEA and gross cystic disease fluid protein-15 (GCDFP-15) suggest an origin from eccrine or apocrine duct epithelium (Table 7-5) (21,261,388,461). CEA is also present in normal eccrine and apocrine ductal epithelial cells, but absent in apocrine glandular epithelium (261,286). Immunohistochemical studies have also demonstrated the presence of epithelial membrane antigen (EMA), as well as low molecular weight keratin; of these, CEA appears to be the most sensitive marker (129). Although useful in diagnosis, these markers do not provide any additional advantages over conventional microscopic analysis in the evaluation of the adequacy of surgical resection margins (129).

DNA aneuploidy of the neoplastic Paget cells, as determined by flow cytometry, is associated with invasive Paget disease, Paget disease with in situ adenocarcinoma of sweat glands, and vascular invasion of the Paget disease. DNA aneuploidy and S-phase, as determined by flow cytometry, have not been demonstrated to be significant in predicting time to recurrence (81).

Ultrastructural Findings. Electron microscopic studies have generally identified features of adenocarcinoma without the cell types intermediate between the Paget cells and the adjacent keratinocytes (21,112,287,368).

Treatment and Prognosis. The clinical evaluation of Paget disease requires biopsy of the lesion for a histopathologic diagnosis. Because vulvar Paget disease can have several origins (see Table 7-4), it is important to evaluate the primary lesion as well as the rectum, anus, bladder, and urethra to determine whether the Paget disease is of cutaneous, anorectal, urothelial, or other origin. The origin of the Paget disease significantly influences the therapy.

The primary treatment of vulvar cutaneous Paget disease is usually wide excision (partial deep vulvectomy) of the involved area to encompass the dermis underlying the lesion. Frozen section examination of the margins of the skin is not of value because recurrence of cutaneous intraepithelial Paget disease is approximately the same in those patients with involved margins and those with negative margins (29a,277a,461). Paget cells are often identified microscopically within clinically normal-appearing skin adjacent to and quite removed from the primary Paget disease (157). These findings suggest that sites of Paget cells without clinically evident Paget disease do not represent areas of Paget disease associated with underlying adenocarcinoma. If an underlying adenocarcinoma is present, it is typically beneath the field of clinically recognizable Paget disease.

The surgery for primary Paget disease should include excision of all clinically visible Paget disease, with a 1- to 3-cm margin of clinically normal adjacent skin. Frozen section margin assessment will not significantly contribute to preventing recurrence (29a,277a). When Paget disease is entirely intraepithelial, the prognosis is excellent, even if local intraepithelial recurrences occur. Some patients have been followed many years without evidence of invasion of the dermis. Wide local excision is effective, and recurrent or persistent Paget disease is treated

effectively by local excision, laser ablation, topical 5-fluorouracil or topical imiquimod cream.

If a focus of invasive Paget disease is found, ipsilateral inguinal-femoral lymphadenectomy may be needed, especially if the tumor is deeper than 3 mm, has vascular space involvement, or the groin nodes are suspicious for tumor. If an underlying skin appendage or Bartholin gland adenocarcinoma is identified, extended partial or total vulvectomy with bilateral inguinal-femoral lymph node resection is the usual treatment (48). When an underlying adenocarcinoma is present, the prognosis is related to the stage of the tumor and the status of the regional lymph nodes, and is usually poor.

Primary Cutaneous (Invasive) Paget Disease (Type 1 Paget Disease)

Cutaneous intraepithelial Paget disease with invasion is characterized by Paget cells that invade the superficial dermis contiguous with the overlying intraepithelial Paget disease (fig. 7-42). The invasive Paget cells lack the orderly arrangement of cells within epithelium. An associated dermal inflammatory response is usual with dermal invasion. The invasive foci are usually irregular in contour, and may consist of single Paget cells in the dermis immediately adjacent to the invasive focus. When the tumor focus is larger, it has features of adenocarcinoma, with the same immunohistochemical findings as seen in intraepithelial Paget cells. Signet ring cells and acinar glandular structures may be seen.

Paget disease as a manifestation of underlying vulvar adenocarcinoma of glandular or skin appendage origin occurs in approximately 5 percent of cases. The Paget disease is typically contiguous with the underlying adenocarcinoma. Slicing the excised vulvar skin specimen containing the Paget lesion in a manner to include the immediate underlying dermis is needed to identify such underlying adenocarcinomas.

Paget Disease Secondary to Rectal or Anal Adenocarcinoma (Type 2 Paget Disease)

Definition. *Paget disease secondary to rectal or anal adenocarcinoma* is an intraepithelial neoplasm characterized by a proliferation of neoplastic glandular type cells that arise and extend from adjacent anal or rectal adenocarcinoma or adenocarcinoma in situ.

General Features. Perianal Paget disease is less frequent than primary cutaneous Paget disease but has similar clinical features. Paget disease that is primarily in a perianal location is usually a manifestation of anal or rectal adenocarcinoma (173), although it may be of primary cutaneous origin. Paget disease of anorectal origin characteristically primarily involves the perianal mucosa and skin, and secondarily involves the vulva. Advanced Paget disease can involve most of the vulva.

Microscopic Findings. Paget cells of anorectal origin have essentially the same morphologic features as those of cutaneous Paget disease. They are distinguished by their expression of CEA, CK7, and CK20, and lack of expression of GCDFP-15 and uroplakin-III (Table 7-5) (302,461).

Treatment and Prognosis. Treatment is directed at the primary rectal adenocarcinoma. Paget disease can be treated by superficial excision (48). The prognosis is related to the extent of the anal or rectal adenocarcinoma. Paget disease may recur and recurrences can be treated with superficial excision, laser ablation, or other methods.

Paget-Like Disease Secondary to Urothelial Neoplasia: Pagetoid Urothelial Intraepithelial Neoplasia (Type 3 Paget Disease: Pagetoid Transitional Cell Neoplasia, Pseudo-Paget Disease)

Definition. *Paget-like disease secondary to urothelial neoplasia (pagetoid urothelial intraepithelial neoplasia* [PUIN]) is an intraepithelial neoplasm characterized by a proliferation of neoplastic urothelial cells from an associated primary bladder and/or urethral neoplasm.

General Features. The primary urothelial neoplasia extends radially from the bladder or urethra to involve the epithelium of the vulvar vestibule. Paget-like disease of the vulva secondary to urothelial neoplasia is an infrequent finding, and few cases have been reported (250,334,461). Urothelial carcinoma involving the perineum and mimicking Paget disease was initially documented in the male in the Second Series Atlas of Tumor Pathology Fascicle, *Tumors of the Urinary Bladder,* by Koss in 1985 (215). The neoplasm presents clinically with involvement of the vulvar vestibule about the urethra, where the involved mucosa appears red and eczematoid. In the later stages, the lesion may

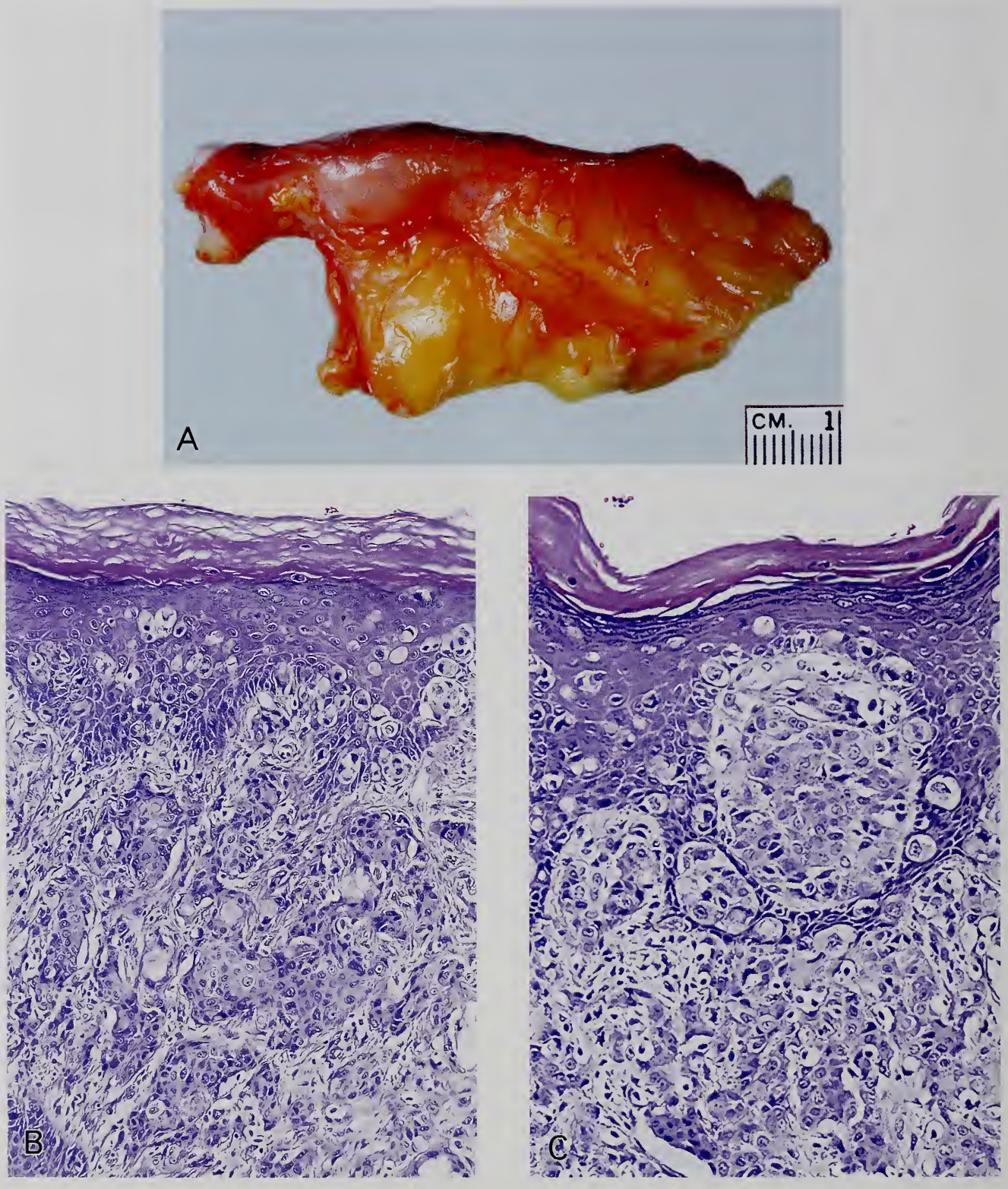


Figure 7-42

PAGET DISEASE, CUTANEOUS TYPE, WITH INVASION

A: A discrete nodule of invasive Paget disease is within the dermis, immediately adjacent to the overlying epithelial surface. (Courtesy of Dr. Brigitte Ronnett, Baltimore, MD.)

B: Invasive Paget disease (adenocarcinoma) with contiguous Paget disease of cutaneous type.

C: The intraepithelial Paget disease is contiguous with the underlying invasive Paget disease.

extend to involve the entire vestibule, vagina, and adjacent vulvar epithelium.

Microscopic Findings. The cells of Paget-like lesions of urothelial neoplasia are clustered or occur singly within the epithelium, as seen with cutaneous Paget disease. Signet ring features are missing, as are intracytoplasmic vacuoles. The nuclei may be as large or larger than the nuclei of the keratinocytes and lack prominent nucleoli (fig. 7-43). A Pap test or cytologic scrapings from the lesion demonstrate single cells and groups of cells that are large, with hyperchromatic and pleomorphic nuclei and small and irregular nucleoli. The cytoplasm is uniform, without vacuoles or inclusions, and displays features of high-grade urothelial neoplasia (43,174).

The immunohistochemical features are distinctive. These cells do not express CEA or GCDFP-15, but express CK7, may express CK20, and express uroplakin III. These findings distinguish it from vulvar cutaneous or anorectal Paget disease (Table 7-5) (44,461).

Treatment and Prognosis. Primary therapy is directed toward treatment of the primary neoplasm. The associated vulvar Paget-like lesion is treated by superficial excision, with or without additional ablative procedures, to preserve the vulvar anatomy (48). Recurrences are treated with superficial excision, laser ablation, or other methods. The prognosis is related to the extent of the urothelial neoplasm.

Differential Diagnosis of Paget Disease and Paget-Like Lesions

Vulvar Paget disease and PUIN must be distinguished histopathologically from vulvar melanoma in situ, VIN, clear cell papulosis, and bowenoid reticulosis. These neoplasms clinically do not usually resemble vulvar Paget disease, although there are histologic similarities. Superficial spreading malignant melanoma, which histologically closely resembles Paget disease, usually express S-100 protein, HMB45, and Melan-A, and does not express cytokeratins, CEA, or uroplakin III.

VIN may histologically simulate Paget disease, particularly when there are large, clear dysplastic squamous cells scattered in a background of normal-appearing squamous cells (388). Stains for mucin and CEA are useful in the differential diagnosis, since Paget cells are positive but not VIN cells.

Clear cell papulosis is a benign localized intradermal proliferation of clear Paget-like Toker cells. This lesion occurs predominately on the lower abdomen of children. The morphologic features suggest Paget disease, however, clinically it does not resemble Paget disease. An apparently related lesion has been described as a Paget-like lesion on the male genital tract (66). These Toker cell–related lesions have tadpole-shaped Paget-like cells, which help to distinguish them from typical cutaneous Paget disease. Toker cells express CEA and cytokeratins (AE1/3), and do not express melanoma-related antigens. Immunohistochemically, Toker cells are not distinguishable from Paget cells, and it has been suggested that Toker cells may be a possible source of cutaneous Paget disease (66).

Bowenoid reticulosis is a lymphoproliferative process that involves the skin. It is an intraepithelial neoplastic accumulation of large pleomorphic lymphocytes that express lymphocyte markers and do not express cytokeratins, CEA, or other related Paget disease markers.

NEOPLASTIC GLANDULAR LESIONS

Bartholin Gland Tumors

Definition. *Bartholin gland tumors* are neoplasms that arise at the site of the Bartholin gland, are consistent histologically with a primary neoplasm of the Bartholin gland, and are not metastatic (55,62,234,453,483).

General Features. Many benign and malignant tumors arise from the Bartholin gland. The benign tumors include *adenomas* and *adenomyomas*; *nodular hyperplasia* has also been reported (211). Adenomas of the Bartholin gland often present as Bartholin cysts, but rarely exceed 2 cm in greatest diameter. Nodular hyperplasia is characterized by a normal duct-acinar relationship and is composed of acini with benign-appearing mucinous epithelium that are lobulated and may be irregular, but are not infiltrative. Ductal squamous metaplasia and ductal inflammation may be present (211).

Bartholin gland adenomas are rare, as are adenomyomas. Adenomas are benign tumors composed of mucinous cells. They lack the apparent duct-acinar relationship, but are not

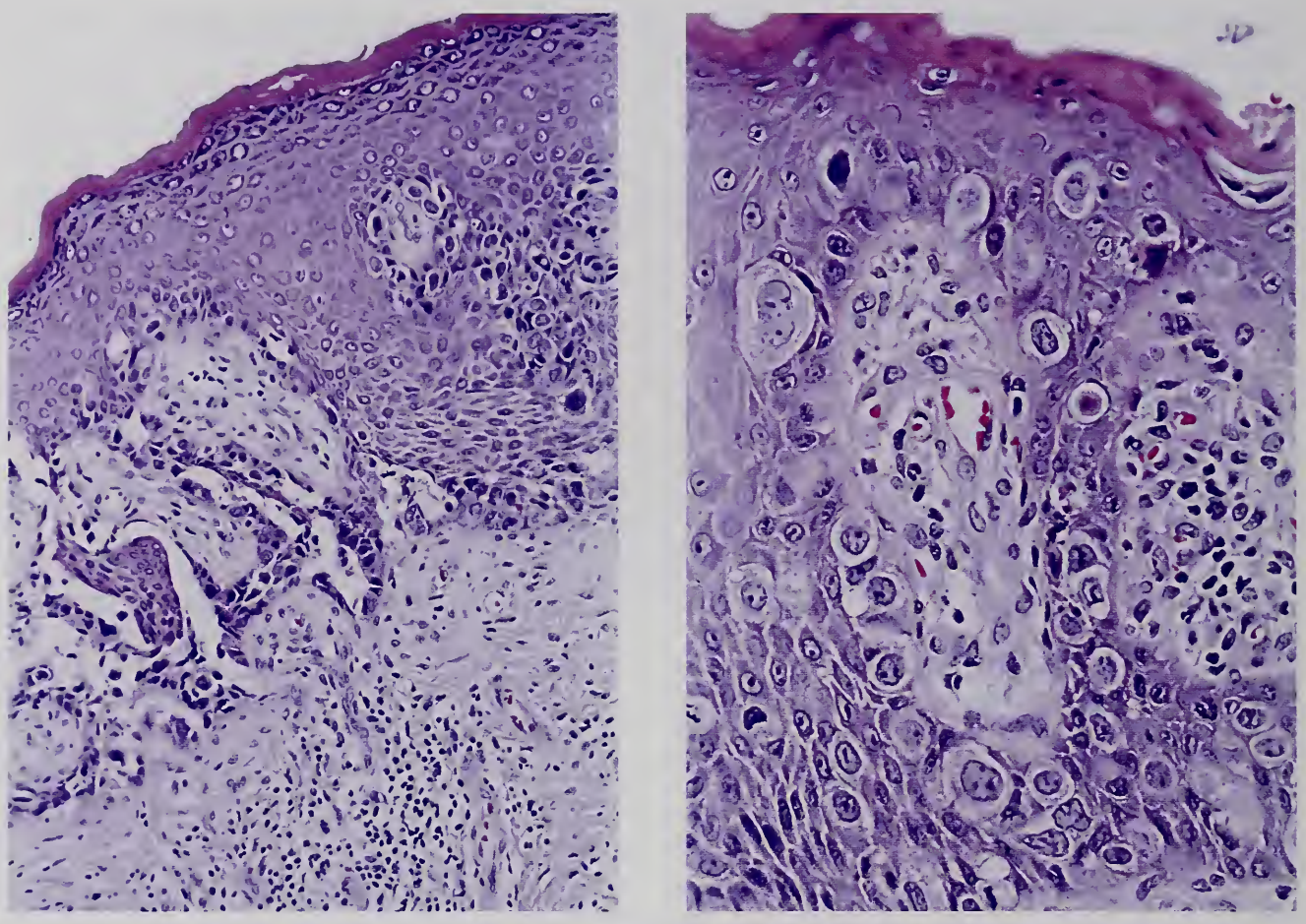


Figure 7-43

PAGET-LIKE DISEASE OF UROTHELIAL ORIGIN (PUIN)

Left: Within the basal and parabasal epithelium, large cells have larger nuclei and paler cytoplasm than the adjacent keratinocytes. These neoplastic Paget-like cells are seen about clefts, an apparent artifact that is a common finding in PUIN lesions.

Right: The Paget-like cells of PUIN are within the basal and parabasal epithelium. They are large, some are binucleated, and most have prominent pale cytoplasm. The nuclei are pleomorphic, have pale nuclear chromatin, and some have prominent nuclei, distinct from the adjacent keratinocytes. There is a moderate superficial dermal chronic inflammatory infiltrate.

infiltrative. Adenomyomas are composed of benign glandular epithelium with a prominent fibromuscular tumor component. These are also benign and not infiltrative. Although experience is limited, adenomas and adenomyomas do not recur once completely excised.

Adenomas and adenomyomas do not express p53 but may have estrogen and progesterone receptors. Occasional cells may express low levels of MIB-1: fewer than 5 percent of the cells of the adenomas studied in one series were positive (211).

Adenocarcinomas account for approximately 40 percent of primary malignant tumors of the Bartholin gland. Other primary tumors include *squamous cell carcinoma* (40 percent), *adenoid cystic carcinoma* (15 percent), *transitional cell carcinoma* (less than 5 percent), *adenosquamous carcinoma* (less than 5 percent), and *poorly differentiated adenocarcinomas* (475,483).

Clinical Features. Carcinoma of Bartholin gland usually presents as a painless enlargement in the gland area and may be mistaken for a cyst (55,258,365). The average age of women with this tumor is 50 years, with the majority occurring in women between 40 and 70 years of age.

Gross Findings. Bartholin gland carcinomas are typically solid, deeply infiltrative, and occupy the site of the gland, occasionally obscuring its presence. They typically range from 1 to 7 cm in diameter.

Microscopic Findings. Adenocarcinomas of the Bartholin gland are usually nonspecific

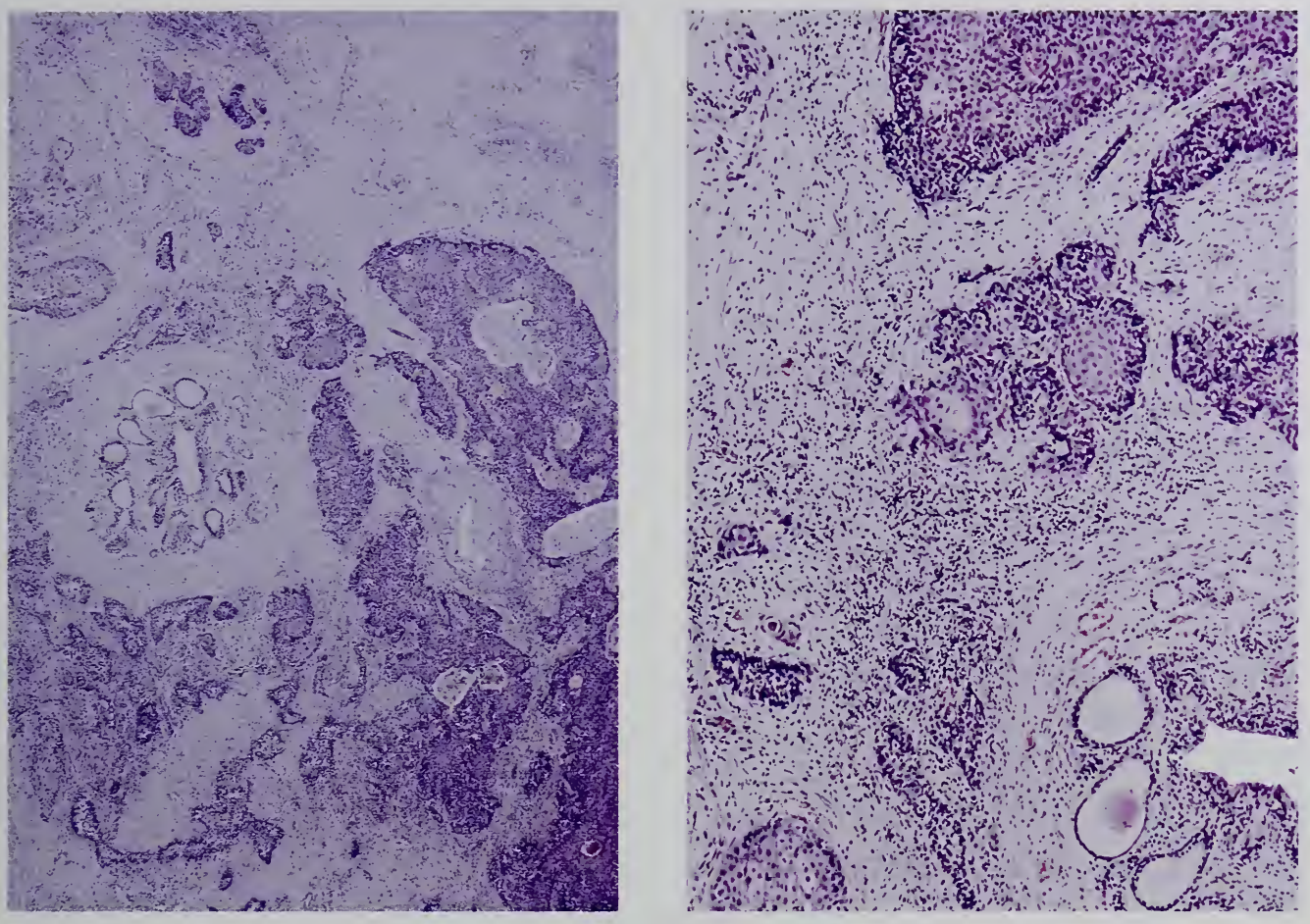


Figure 7-44

SQUAMOUS CELL CARCINOMA OF THE BARTHOLIN GLAND

Left: Portions of the gland and duct lie adjacent to the poorly differentiated squamous cell carcinoma, which is associated with moderate inflammatory infiltration of the stroma.

Right: Bartholin duct is adjacent to the invasive nonkeratinized squamous cell carcinoma. There is a moderate inflammatory infiltrate in the adjacent dermis.

in appearance, but mucinous and papillary types have been described (fig. 7-44) (62). The tumors usually contain intracytoplasmic mucin and are immunoreactive for CEA (284, 285). Salivary gland–like adenocarcinomas have been described in the vulva, including a polymorphous low-grade adenocarcinoma that resembled adenoid squamous cell carcinoma but contained cribriform, cystic and papillary components with empty or minimal intraluminal secretion, and hybrid adenocarcinoma with associated adenoma (314,481).

Squamous cell carcinomas arising in the Bartholin gland have the same microscopic appearance as those arising elsewhere in the vulva. These tumors are typically immunoreactive for CEA (284).

Adenoid cystic carcinomas arising in the Bartholin gland are composed of uniform, small cells arranged in cords and nests with a cribriform pattern (fig. 7-45). Variable-sized cysts filled with amphophilic or eosinophilic, acellular basement membrane–like material (1,8,79,91,475) may also be encountered. Keratin and S-100 protein antigen are detectable by immunohistochemistry (284). The S-100 protein reactivity may demonstrate a myoepithelial cell element. Approximately 40 percent of the adenoid cystic carcinomas are immunoreactive for p53 (211). Ultrastructural features include basement membrane–like material within the cysts (220). Adenoid cystic carcinoma has been reported associated with a Bartholin gland adenoma (314). This tumor had features of a

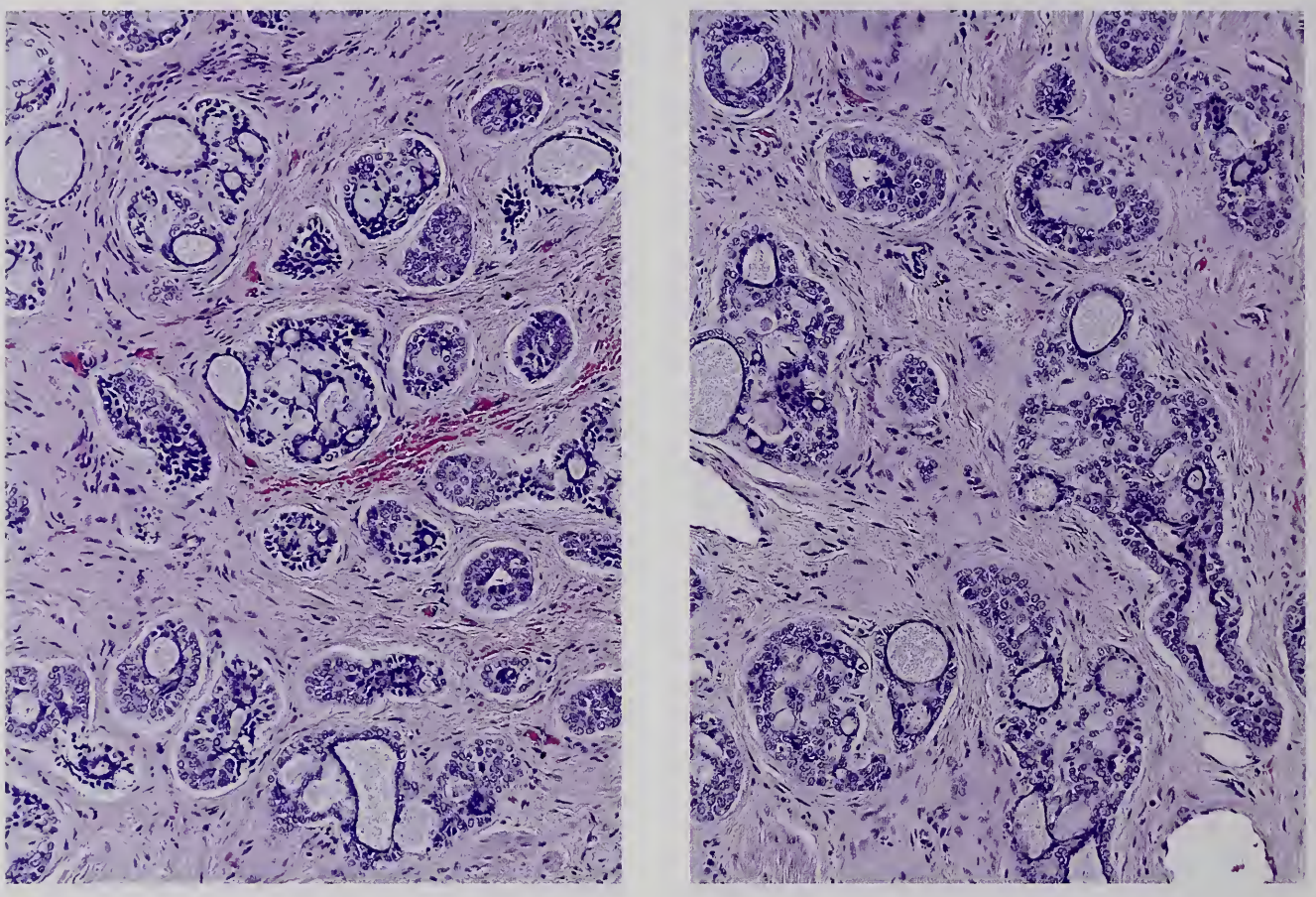


Figure 7-45

ADENOID CYSTIC CARCINOMA OF BARTHOLIN GLAND

Left: The variably sized groups of tumor cells form a cribriform pattern. Adjacent Bartholin gland acini are seen.
Right: The tumor cells are small and uniform. Acellular material is seen within the rounded spaces. (Left and right courtesy of Dr. Yao S. Fu, Los Angeles, CA.)

salivary gland-like "hybrid" carcinoma, and contained two morphologically different tumors with the same origin and location. The differential diagnosis of adenoid cystic carcinomas includes usual adenocarcinoma, polymorphous low-grade adenocarcinoma, basal cell carcinoma, metastatic atypical carcinoid, and small cell carcinoma. Adenocarcinomas lack the uniform acinar arrangement and intraluminal basement membrane material of adenoid cystic carcinoma. Basal cell carcinomas are more solid, and lack the cystic spaces and intracystic basement membrane–like material. Metastatic carcinoids and small cell carcinomas are more solid, have fewer lumens, contain argyrophil cells, and stain for neuron-specific enolase in most cases. Carcinoids almost always react with antibodies against chromogranin and other neuroendocrine markers.

Adenosquamous carcinomas of Bartholin gland contain a mixture of squamous cells, identified by keratin formation and intracellular bridges, and glandular cells that typically contain mucin (190,429).

Transitional cell carcinomas arising in the Bartholin gland are composed of uniform polyhedral or rounded epithelial cells that often line broad papillary fronds. Rare areas of glandular or squamous differentiation are found. The differential diagnosis includes poorly differentiated squamous cell carcinoma and adenocarcinoma. If more than rare foci contain glands or show keratinization, the tumor is of mixed cell type and should be so designated, with a listing of the different tumor types.

Squamous intraepithelial neoplasia associated with HPV type 16 has been reported within a Bartholin duct gland cyst (390).

Differential Diagnosis. The differential diagnosis of the Bartholin gland adenocarcinoma includes adenocarcinoma of skin appendage origin and metastatic adenocarcinoma. Such tumors typically do not obscure the Bartholin gland. The tumor type, other than for squamous cell carcinoma, is usually not consistent with a primary tumor of the Bartholin gland.

Metastatic tumors can involve the Bartholin gland. Breast carcinoma, including lobular adenocarcinoma, has been documented to be metastatic to the Bartholin gland area (267a) Primary vaginal tumors involve the Bartholin gland, and small cell carcinoma of the vagina has also been reported (274).

Treatment and Prognosis. The primary treatment for a Bartholin gland carcinoma is partial deep vulvectomy or total deep vulvectomy. Ipsilateral or bilateral inguinal-femoral lymph node dissection is necessary in most cases, regardless of the type of primary excision (1,79,453).

The 5-year survival rate of patients with Bartholin gland carcinomas is approximately 50 percent when the groin nodes are free of tumor, but decreases to 18 percent when two or more nodes are involved (62,234,453). Approximately 20 percent of primary carcinomas of the Bartholin gland are associated with metastases to the inguinal-femoral lymph nodes. If the groin nodes are involved, there is a 20 percent probability that pelvic lymph node metastasis is also present, but if they are free of metastasis, there is essentially no risk of pelvic node metastasis (62). In more advanced cases, adjuvant radiotherapy is commonly used, however, in one study, 71 percent of the patients who had adjuvant radiation therapy had recurrence (55). A limited study employing radiation therapy and chemotherapy with cisplatin and 5-fluorouracil has shown promising results (259).

Therapy for adenoid cystic carcinoma of the Bartholin gland is surgical. In a literature review, radical vulvectomy (total deep vulvectomy) with negative margins appeared preferable to wide local excision (partial deep vulvectomy) as primary therapy (8). Inguinofemoral lymphadenectomy was applicable only when the lymph node was suspicious by clinical examination. Wide local excision with ipsilateral inguinal-femoral lymphadenectomy has also been used (79). There is sufficient evidence to state that survival is better with adenoid cystic carcinoma than with other types of carcinoma of the Bartholin gland.

The treatment of vulvar adenosquamous carcinoma is similar to that of squamous cell carcinoma (429). Patients with adenosquamous carcinoma have a poorer prognosis than those with squamous cell carcinoma, with a reported 5-year survival rate of 66 percent. The poorer prognosis is in part related to the higher frequency of lymph node metastasis.

Malignant Mixed Tumor

Malignant mixed tumor has been reported as a primary tumor of the vulva (408a). Metastases from a malignant mixed tumor are usually composed of epithelial elements only. There are insufficient cases of vulvar mixed tumor to determine its natural history in this site. Wide local excision is the recommended therapy for both the primary tumor and local recurrences.

Mammary Gland–Like Adenocarcinoma and Other Mammary-Like Tumors Arising in the Vulva

Mammary gland-like tumors of the vulva are well recognized, and although once thought to arise from ectopic breast tissue, there is evidence that specialized anogenital mammary gland-like glands, found typically in the interlabial sulcus, are the origin of vulvar mammary gland-like benign tumors and adenocarcinomas (434,435). *Fibroadenomas* (238), *intraductal papillomas* (358), and *lactating adenomas* have been described arising in the vulva. *Cystosarcoma phyllodes* arising in the vulva has also been described (271).

A report of intraductal carcinoma of mammary type arising in a papillary hidradenoma of the vulva has helped support the concept of origin (324). *Papillary hidradenoma* and *fibrocystic-like disease* have been described within these specialized glands.

Adenocarcinomas arising in specialized anogenital glands have features similar to those of primary mammary adenocarcinoma: infiltrating, well-differentiated adenocarcinoma and occasionally an intraductal carcinoma component are identified (67,92,153,395). Metastasis to inguinal lymph nodes can occur (67). These adenocarcinomas contain alpha-lactalbumin

and milk fat globulin protein. They may express estrogen and progesterone receptors (ER, PR).

Tumors that arise in mammary-like tissue typically occur in the intralabial sulcus or the immediately adjacent labium majus or minus. Fibroadenomas are distinguished from tumors of sweat gland origin by the adjacent mammary gland-like tissue and characteristic features of a fibroadenoma (117). Intraductal papillomas may mimic hidradenoma to the degree that the two cannot be distinguished microscopically (358). Unlike carcinomas arising in ectopic breast tissue, metastatic carcinomas to the vulva are not associated with adjacent mammary gland-like tissue and are usually larger (244,262).

Mammary gland-like tissue within the vulva may need to be excised if a symptomatic mass occurs when the patient is not pregnant. Enlargement during pregnancy is usually related to physiologic changes and observational management is applicable. The presence of a malignant tumor within mammary gland-like tissue usually requires partial deep vulvectomy and inguinal-femoral lymphadenectomy.

Adenocarcinoma of Cloacogenic Origin (Mucinous Adenocarcinoma Arising in the Surface Epithelium of the Vulva)

Adenocarcinoma of cloacogenic origin is a mucinous tumor that arises in continuity with the overlying epithelium and invades the underlying dermis. These tumors are typically not associated with underlying dermal neoplastic glandular elements, although benign-appearing mucinous glands have been observed in the dermis deep to the tumor in one case (482). Adenocarcinoma of cloacogenic origin is rare, with approximately 10 cases reported.

The tumor presents as a cutaneous mass that can be polypoid, excoriated or inflamed. Microscopically, these tumors are mucinous adenocarcinomas, usually of colonic epithelial type, with goblet cells and intracytoplasmic mucin (fig. 7-46). Apocrine differentiation is not present (204,421,482). The tumors are immunoreactive with mucicarmine, Alcian blue pH 5, polyclonal CEA, CK17, CAM 5.2, and p53 antigen. S-100 protein and chromogranin are also immunoreactive in some cells within the epithelium, consistent with the presence of endocrine cells. The tumors are monoclonal CEA and ER and PR negative. Electron microscopic studies have demonstrated a colonic type epithelium (469,482).

Although there is limited experience, these tumors have not metastasized to regional nodes. Most patients are treated with partial deep vulvectomy (deep local excision) and have done well (469).

Carcinoma of Sweat Gland Origin

Carcinoma of sweat gland origin accounts for less than 1 percent of all vulvar cancers (455). Patients usually present with a painless vulvar mass (271). *Undifferentiated sweat gland adenocarcinomas*, as well as *ductal eccrine adenocarcinoma, eccrine porocarcinoma, clear cell hidradenocarcinoma, apocrine carcinoma*, and *adenocarcinoma arising in chondroid syringoma* have been reported (130,455).

A number of vulvar apocrine carcinomas have been associated with vulvar Paget disease (271). Apocrine carcinoma is composed of tumor cells with a distinctive eosinophilic granular cytoplasm and may be associated with apocrine decapitation type secretion. The tumor has solid, glandular, or papillary areas. Nuclear pleomorphism and hyperchromasia are present.

Sebaceous carcinoma of the vulva, which may be associated with VIN, has also been reported (105,455). A vulvar sweat gland undifferentiated carcinoma resembling *epithelioid sarcoma* arising in the labium majus had nodular growth in the superficial dermis with central hemorrhage and necrosis (217). In some areas of the tumor, cells had rhabdoid features and in other areas, the tumor cells were separated by mucinous-like stroma. The tumor had an epithelial cell population with florid geographic necrosis resembling that of epithelioid sarcoma. The tumor expressed CAM 5.2, EMA, and CEA, as well as sweat gland type reactivity (immunoreactive for CA125, EKH5, and EKH6). Electron microscopic features also demonstrated sebaceous glandular features. Survival following surgical excision was reported at 8 months.

Mucinous Eccrine Carcinoma with Neuroendocrine Differentiation

Mucinous adenocarcinoma analogous to cutaneous mucinous carcinoma, *with associated neuroendocrine differentiation*, has been reported arising in the vulva (134,343). The tumor presents as a

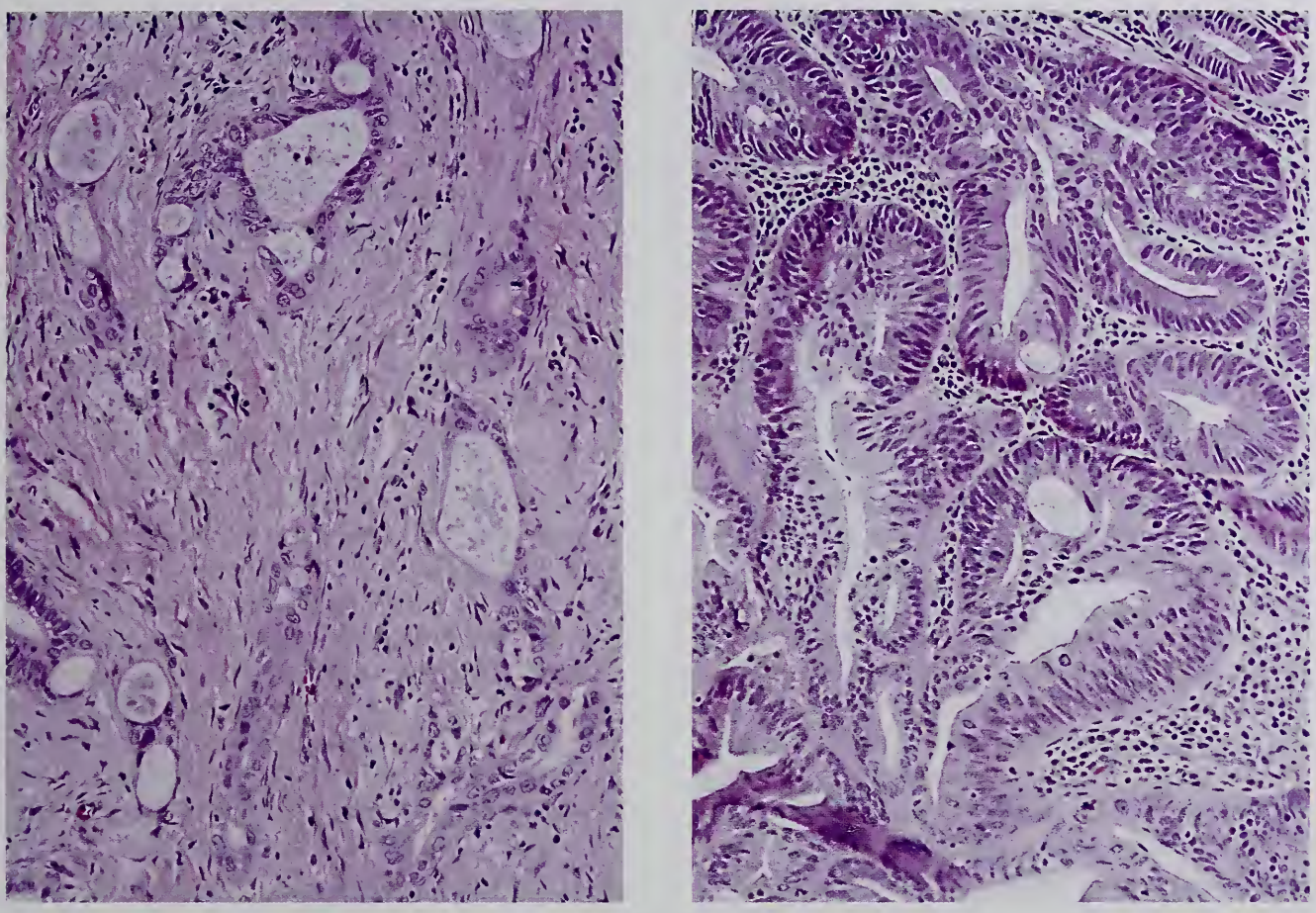


Figure 7-46

MUCINOUS ADENOCARCINOMA OF THE VULVA

Left: The neoplastic glands are variably shaped and produce mucin. There is an associated dermal desmoplastic change, with mild chronic inflammation.

Right: Well-differentiated neoplastic glands have epithelial cells that secrete mucin as well as features of an an adenocarcinoma of enteric origin. Signet ring cells and goblet cells are not present. (Left and right courtesy of Dr. Ricardo Ramos, Jacksonville, FL.)

polypoid or ulcerated mass in the labium majus or the posterior fourchette. The adenocarcinoma resembles colonic adenocarcinoma and in one case was associated with an apparent villous adenoma (134). Pools of mucin may surround tumor cell groups (343). The tumor contains mucin-producing and neuroendocrine type cells. The latter are identified with immunohistochemical studies for neuron-specific enolase, S-100 protein, and chromogranin, as well as by electron microscopy. The epithelial elements are immunoreactive for CAM 5.2 and AE1/3 (343).

Mucinous Adenocarcinoma with Focal Squamous and Neuroendocrine Differentiation

A *mucinous adenocarcinoma with focal squamous and neuroendocrine differentiation* arising in the labium majus has been reported (145). The tumor expressed chromogranin A, protein gene product 9.5, serotonin, and vasoactive intestinal polypeptide.

BENIGN MESENCHYMAL TUMORS

Benign mesenchymal tumors are not specific to the vulva and occur, for the most part, in other sites. For a more detailed discussion, the reader is referred to other references on soft tissue tumors.

Lipoma/Fibrolipoma

A *lipoma* is a benign tumor composed of mature adipocytes. When the tumor contains prominent fibroblasts and collagen, it is termed a *fibrolipoma.* Lipomas of the vulva are rare. They are typically

encountered in adults, usually presenting as soft, circumscribed masses of variable size in the labium majus. A vulvar lipoma presented in a neonate, mimicking ambiguous genitalia (436). Lipomas grow slowly and may present with hemorrhagic infarction or surface ulceration.

Lipomas are composed of mature adipocytes supported by fibrovascular tissue. The adipocytes contain S-100 protein antigen (238). Nevus lipomatous superficialis, an entity that should be distinguished from lipoma, also contains adipose tissue within the dermis. In contrast to a lipoma, the adipose tissue in nevus lipomatous superficialis is limited to the superficial dermis and distinct from the underlying subcutaneous fat.

Intradermal Spindle Cell (Pleomorphic) Lipoma of the Vulva

Intradermal spindle cell lipoma, also termed *pleomorphic lipoma,* is a benign intradermal tumor of adipose origin. It is rare on the labium majus (354). The tumor is superficial and composed of spindle-shaped cells arranged in short fascicles with mature adipocytes and some lipoblasts. Multinucleated floret-like giant cells are present. The tumor may be poorly demarcated, with infiltrative-appearing margins. Involvement of dermal nerves may occur.

The spindle cells are immunoreactive for CD34 and the adipocytes and spindle cells are immunoreactive for S-100 protein and vimentin. Treatment is local excision (partial deep vulvectomy), although experience is limited.

Lipoblastoma-Like Tumor of the Vulva

Lipoblastoma-like tumor of the vulva is a benign tumor with adipocytic differentiation. It is rare and has been described in adolescents and women of reproductive age. The tumor presents as a mass in the labia majora and Bartholin area, and can measure up to 10 cm in greatest dimension.

On microscopic examination, the tumor is well circumscribed and forms lobules with intervening fibrous septa and a "chicken wire"–like vascular component. The tumor is primarily composed of spindle cells with finely granular eosinophilic cytoplasm and uniform nuclei. Nuclear atypia and mitotic figures are not evident. Signet ring type lipoblasts may be seen, and entrapped mature adipocytes are present. There is no tumor necrosis. The tumor is immunoreactive for vimentin, but negative for CD34, desmin, and smooth muscle actin (222).

Cytogenetic studies have demonstrated rearrangement of the 8q11-q13 region in chromosome 8. This finding may be of value in distinguishing lipoblastoma from liposarcoma, where reciprocal translocation of 12;16 is observed as well as expression of the TLS/FUS-CHOP fusion oncoprotein (222).

Treatment is local excision (partial deep vulvectomy). Recurrences have not been reported; however, experience is limited (222).

Nevus Lipomatosis Superficialis

Nevus lipomatosis superficialis is a congenital superficial connective tissue hamartoma, usually found on the medial aspects of the thigh or buttock, and occasionally found on the vulva. Clinically, nevus lipomatosis superficialis is plaque-like or sessile, soft, and covered by normal-appearing skin. On microscopic examination, the lesion is composed of mature fat confined within the superficial dermis, and distinct from the underlying subcutaneous fat. No other hamartomatous elements are associated with this nevus.

Hemangioma

Hemangiomas are benign vascular tumors. They are rare in the vulva. They occur at any age, but specific types are usually confined to the very young or old (133). Although hemangiomas may become ulcerated and bleed, they generally regress spontaneously and do not require treatment (133). An *arteriovenous hemangioma* of the vulva presented with cyclic swelling of the labium majus; it regressed following menstruation and required excision for cure (226).

Capillary Hemangioma (Strawberry Hemangioma, Juvenile Hemangioma)

Capillary hemangioma, also termed *strawberry hemangioma* or *juvenile hemangioma*, is most commonly encountered in infants and young children. It is a soft, red to violaceous, slightly raised, well-demarcated lesion. It occasionally bleeds due to ulceration or trauma. Usually it does not exceed 1 cm in diameter. The clinical appearance of this lesion is usually sufficiently typical to make biopsy unnecessary.

Microscopic examination discloses a well-circumscribed mass composed of a dense aggregate

of capillaries. Because it usually regresses spontaneously, therapy is rarely necessary.

Cavernous Hemangioma

Cavernous hemangioma is rare in the vulva. It is typically deeper, more complex, and larger than capillary hemangioma. Pelvic involvement may occur concurrently (310). Biopsy is not indicated unless ulceration or other clinical features suggest malignancy. Cavernous hemangioma of the clitoris may mimic clitoral hypertrophy (201), suggesting adrenogenital syndrome in a young child.

Acquired Hemangioma

Vulvar *acquired hemangioma* of adults typically occurs in older women and is relatively common, although rarely biopsied. It usually presents as multiple, 1 to 3 mm, purple to red, asymptomatic papules on the lateral aspects of the labia majora. On microscopic examination the mass is well circumscribed and composed of aggregated capillaries, some of which may be dilated.

The differential diagnosis of hemangioma includes angiokeratoma, pyogenic granuloma, bacillary angiomatosis, hemangiopericytoma, angiosarcoma, and Kaposi sarcoma (73,87,238). Angiokeratoma is a warty or polypoid lesion characterized by an acanthotic, slightly hyperkeratotic epidermis overlying dilated capillary spaces. Pyogenic granuloma is superficial, resembles granulation tissue, and has a distinctive collarette of elevated epithelium around it. A Warthin-Starry stain identifies the *Bartonella (Rochalimaea) henselae* bacteria within bacterial angiomatosis (73,352). Hemangiopericytoma is a solid vascular tumor with a distinctive perivascular pericyte proliferation, demonstrated by a reticulin stain. Kaposi sarcoma is a malignant vascular tumor that has distinctive slit-like spaces containing red blood cells surrounded by malignant spindle cells.

Angiokeratoma

Angiokeratoma is common on the vulva of women of childbearing age, although it is infrequently reported (266). The lesion may be single or multiple, and primarily involves the clitoris. Clinically, angiokeratoma is usually dark red to brown-black, with a warty or polypoid appearance. It is usually slightly larger than acquired hemangioma and may be ulcerated.

Histologic examination reveals superficial vascular channels that lie adjacent to the basal cells of the overlying epithelium (fig. 7-47). The epithelium is often acanthotic and hyperkeratotic. Angiokeratomas do not require treatment unless the patients are symptomatic.

Pyogenic Granuloma

Pyogenic granuloma (granuloma pyogenicum) is a solitary, rapidly growing, raised vascular lesion considered to be a hemangioma variant. It is rare on the vulva, and usually occurs during gestation.

Microscopic examination shows a lobulated capillary hemangioma composed of multiple, small endothelial-lined vessels (fig. 7-48). A prominent inflammatory cell infiltrate may be seen, especially near the surface, if ulceration or secondary infection is present. The surface epithelium may proliferate, with downward growth forming a collarette around the lesion. Excisional biopsy is therapeutic.

Lymphoid Hamartoma

Benign *lymphoid hamartoma* has been reported in the labia majora. It presents as an asymptomatic subcutaneous mass (205).

Microscopically, the lesion is characterized by apparent fibrous encapsulated lymphoid tissue without lymphoid sinusoids. In other sites, lymphoid hamartoma is associated with hypergammaglobulinemia and chronic anemia. Treatment is excision of the lesion.

Superficial Angiomyxoma

Superficial angiomyxoma is a benign tumor with fibroblastic features that involves both the dermis and subcutaneous tissue. It may be associated with Carney complex, in which case the lesions are multiple. The tumor is usually painless and presents as a superficial nodule, papule, or polypoid vulvar mass, 1 to 9 cm in diameter. Most tumors occur in women between 40 to 50 years of age (114,298).

Histologically, the tumor is poorly circumscribed, with a lobular appearance, myxoid stroma, and numerous small vessels, some of which are curved. The cells of the tumor are round to stellate and spindle shaped, and some are multinucleated. Mitoses are infrequent. Cellularity is variable, with hypocellular areas, mucin pools,

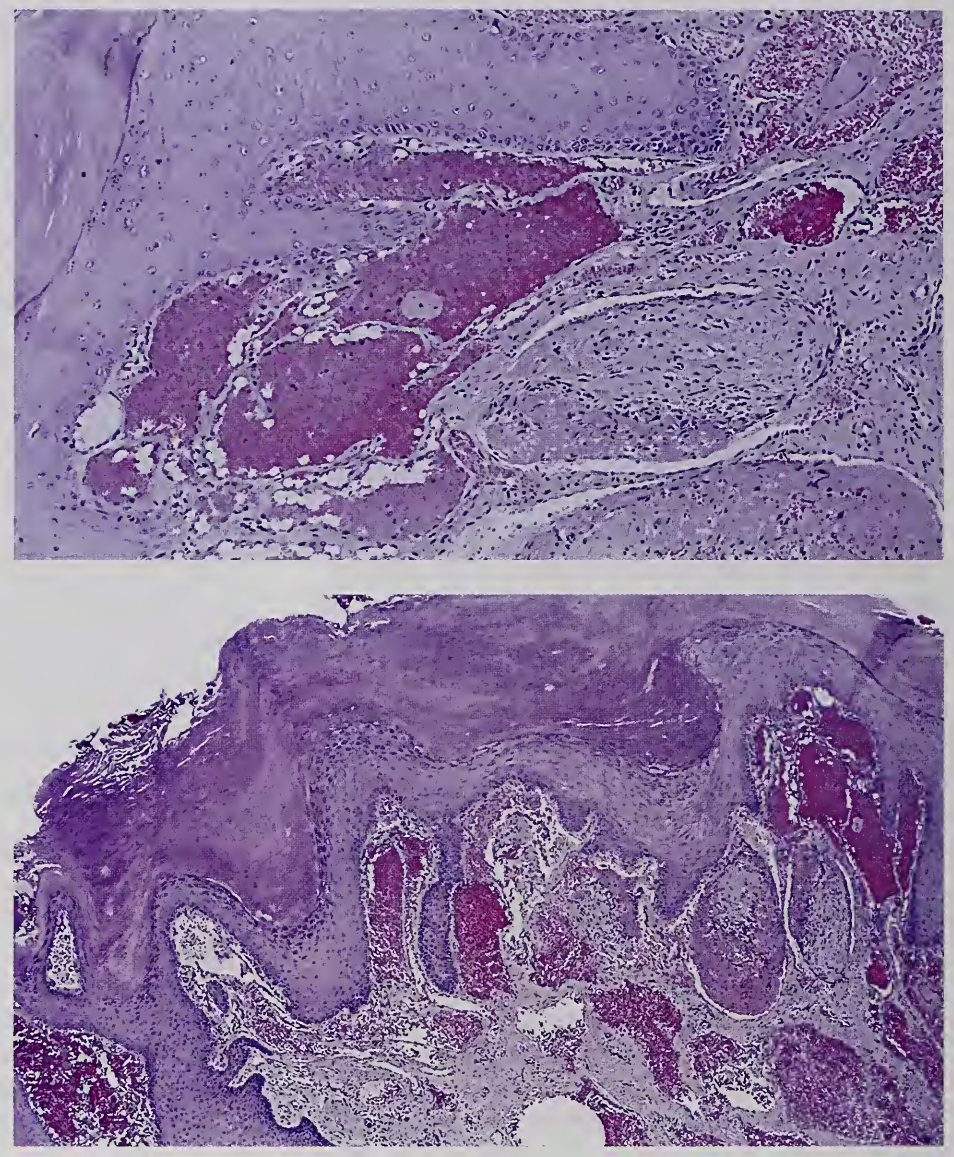


Figure 7-47

ANGIOKERATOMA

Top: Prominent dilated blood-filled vessels are present within the dilated dermal papillae. The vascular endothelium lies adjacent to the overlying acanthotic epithelium.

Bottom: The epithelium is hyperplastic and hyperkeratotic. Prominent, dilated, blood-filled vessels are present within the superficial dermis immediately beneath and abutting the epithelial basement membrane.

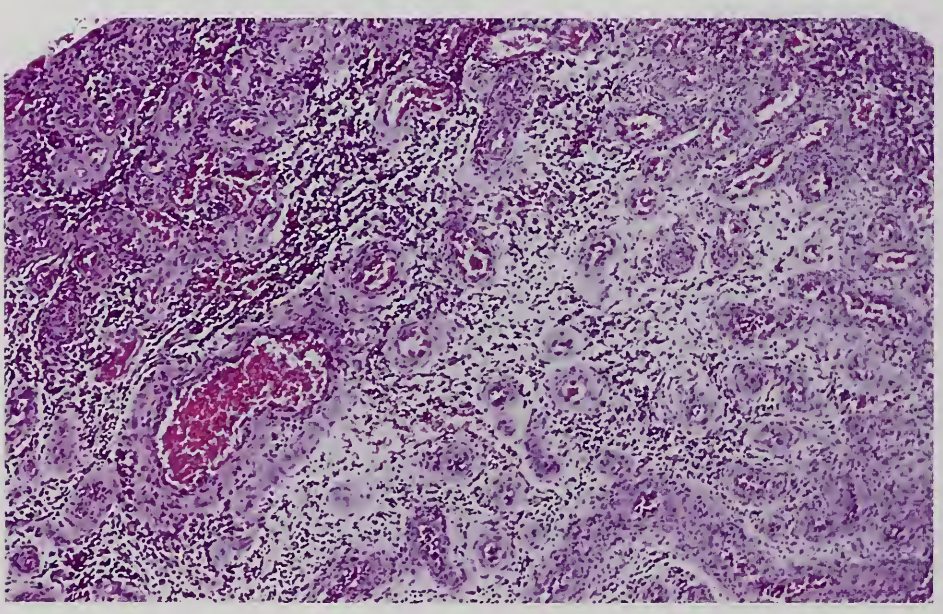


Figure 7-48

PYOGENIC GRANULOMA

The section is from the edge of the lesion. The surface epithelium is partially ulcerated; within the dermis, the vascular lobule is composed of numerous small branched vessels. Many endothelial cells line the small vessels and contribute to the cellular appearance of the lesion. Chronic inflammatory cells are present in the adjacent dermis.

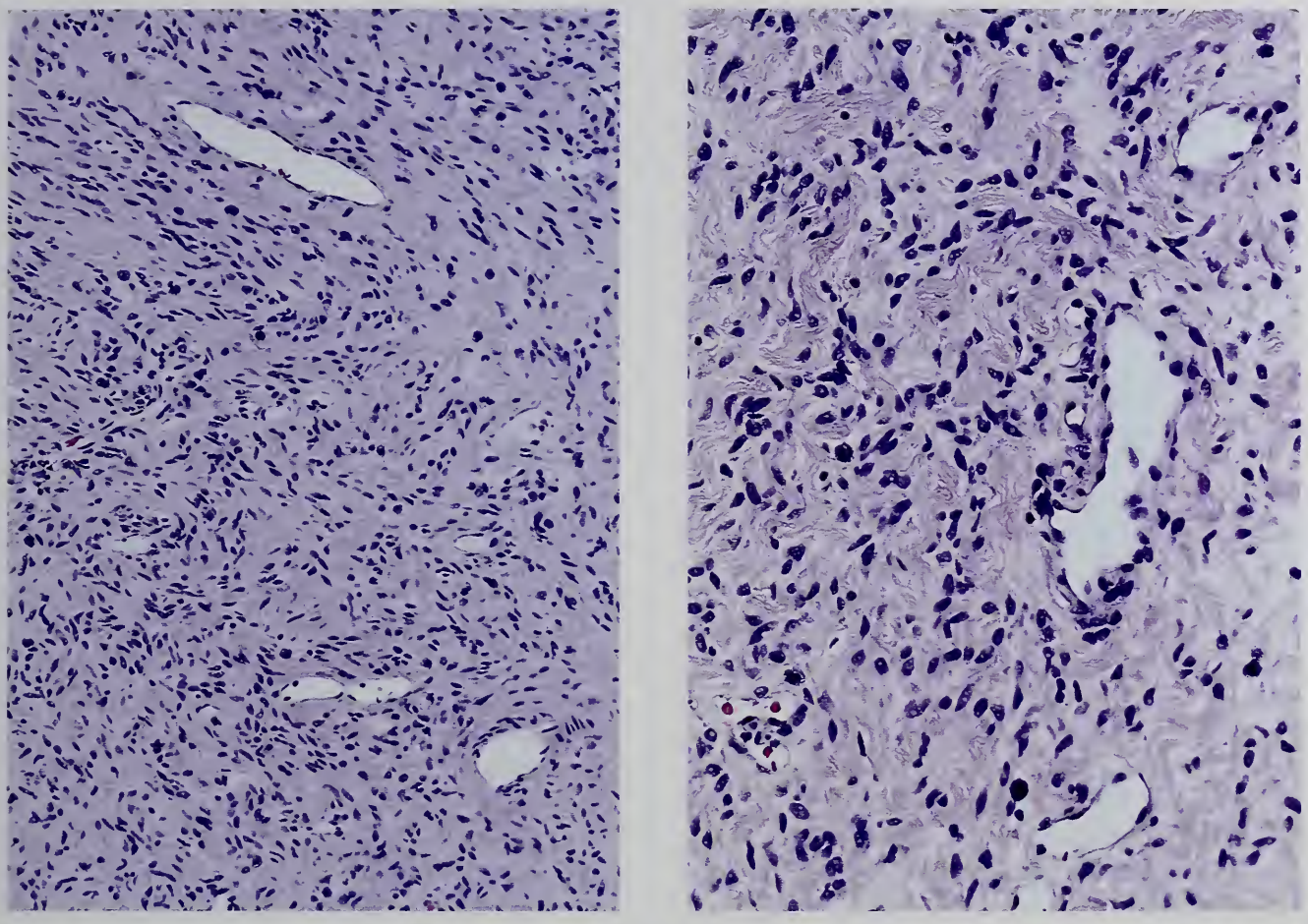


Figure 7-49

ANGIOMYOFIBROBLASTOMA

Left: The tumor contains some medium-sized and numerous capillary-like vessels. The nuclei are uniform with little atypia; some cells are binucleated and multinucleated. The cytoplasm is pale and eosinophilic. Mitotic figures are infrequent.

Right: In perivascular areas, the tumor is more cellular. Hypocellular areas are more peripheral to the vascular areas. The tumor cells about vessels are plump. There are some lymphocytes and mast cells.

muciphages, and a sparse inflammatory cell infiltrate that consists predominately of neutrophils. In some cases, trapped adnexal epithelial elements, including squamous and basaloid cell groups and epithelial-lined cysts, are seen (53). Superficial angiomyxoma is immunoreactive for vimentin, CD34, muscle-specific actin and smooth muscle actin, S-100 protein, and factor XIIIa (114).

Local excision is diagnostic and therapeutic. Superficial angiomyxoma can recur locally.

Angiomyofibroblastoma

Angiomyofibroblastoma is a benign tumor that is reported predominantly on the vulva in middle-aged women. The age range is 23 to 86 years of age, with a mean of 45.8 years. Angiomyofibroblastoma often presents as a painless mass of 0.5 to 12.0 cm, that may clinically resemble a Bartholin cyst (115,176,295,298,300,304). The tumor is soft and on cut section is homogeneous in consistency and pale pink to gray.

Microscopically, the tumor is circumscribed and contains numerous capillary-like vessels, some of which may be branched or ectatic. Some medium-sized vessels may be seen (fig. 7-49). The tumor has hypocellular areas composed of spindled-shaped cells, which may be associated with inflammatory cells and collagen fibers, and hypercellular areas with plump oval cells, some of which have a plasmacytoid appearance. All the tumor cells have uniform nuclei with little atypia and eosinophilic cytoplasm. Binucleated and multinucleated cells may be present. Mitotic

figures are infrequent. In perivascular areas, the tumor is usually more cellular, with hypocellular areas more peripheral to the vascular areas. The stromal cells about vessels are usually plump. Collagen is prominent in some areas. Lymphocytes and mast cells are present in most cases, typically in the hypocellular areas.

A *lipomatous angiomyofibroblastoma* has been described (54,223,295). Malignant transformation of this tumor has been reported, associated and apparently giving rise to a high-grade angiomyofibrosarcoma (295).

The tumor cells are reactive for vimentin and usually express ER and PR. Some cells display variable reactivity with desmin, muscle-specific actin, and smooth muscle actin. The CD34 reactivity that has been reported may suggest a fibroepithelial polyp (223,298,446). Lipomatous angiomyofibroblastoma consists of up to 80 percent fat tissue. In the two reported cases, bcl-2 was positive, and in one case, S-100 protein and CD10 were immunoreactive in one of the two (54).

Ultrastructural studies demonstrate intracytoplasmic intermediate filaments which, in the plump stromal cells, are clustered, giving them a plasmacytoid appearance. The apparent multinucleated cells are actually clustered single cells (295).

The differential diagnosis is primarily aggressive angiomyxoma, which, in contrast to angiomyofibroblastoma, is less cellular, has fewer and larger vessels, some with thick walls and hyalinization, and is locally invasive. Immunohistochemical studies have not been proven useful to date to distinguish these two entities. Composite tumors containing both tumor types have been reported (147). Atypical myxoid fibroepithelial stromal polyp has cellular atypia without hypercellularity, and is not immunoreactive for CD34 (317).

With small tumors, excision is both diagnostic and therapeutic. With larger tumors, the diagnosis depends on biopsy evaluation, followed by local excision.

Aggressive Angiomyxoma

Aggressive angiomyxoma is a locally aggressive mesenchymal tumor. This rare tumor occurs predominately in women of reproductive age, with the highest incidence in the fourth decade (20,87,113,147,263,300,304,307).

Aggressive angiomyxoma is a soft subcutaneous mass that may mimic a Bartholin cyst or suggest a hernia sac. It may extend paravaginally into the pelvic floor or buttocks.

The tumor is usually between 5 to 10 cm in diameter, although much larger tumors have been described (85). It has a uniform, soft consistency. On cut section, the tumor has a blue-gray glistening myxoid appearance; prominent small vessels are visible grossly within the myxoid mass. Hemorrhagic and cystic areas may be identified. The tumor usually has ill-defined boundaries and, although it may appear partially encapsulated, is typically poorly circumscribed and blends into the surrounding tissue.

Aggressive angiomyxoma consists of numerous nonarborizing blood vessels, particularly capillaries and medium-sized arteries, some with thick muscle walls (fig. 7-50). Small smooth muscle cell groups may be seen adjacent to these muscular vessels. The bulk of the tumor is composed of fibroblasts and myofibroblasts, which are spindle shaped to stellate, with small uniform nuclei (sometimes multinucleated) containing dense chromatin and small nucleoli; pseudoinclusions may be present. Mitotic figures and nuclear pleomorphism are rare. The tissue surrounding the cells is myxoid in some areas and densely collagenous elsewhere. Nerves and epithelial elements may be entrapped, with mucin-secreting columnar cells forming small glandular structures.

The tumor cells are immunoreactive for vimentin and usually express desmin, smooth muscle actin, muscle-specific actin, CD34, and ER and PR (113,147,263,307). The endothelium of the blood vessels reacts with factor VIII–related antibodies. Other than the occasional epithelial elements that may be found in these tumors, the tumor does not express S-100 protein antigen, CEA, or keratin. Cytogenetic studies have demonstrated chromosome translocation t(85;113) with *HMGIC* gene alterations in aggressive angiomyxoma (307).

The main entity in the differential diagnosis is angiomyofibroblastoma, a tumor that appears to be related to aggressive angiomyxoma (147). Angiomyofibroblastoma has well-defined borders, is typically not infiltrative, and has larger tumor cells, some of which are epithelioid or plasmacytoid. Composite tumors consisting

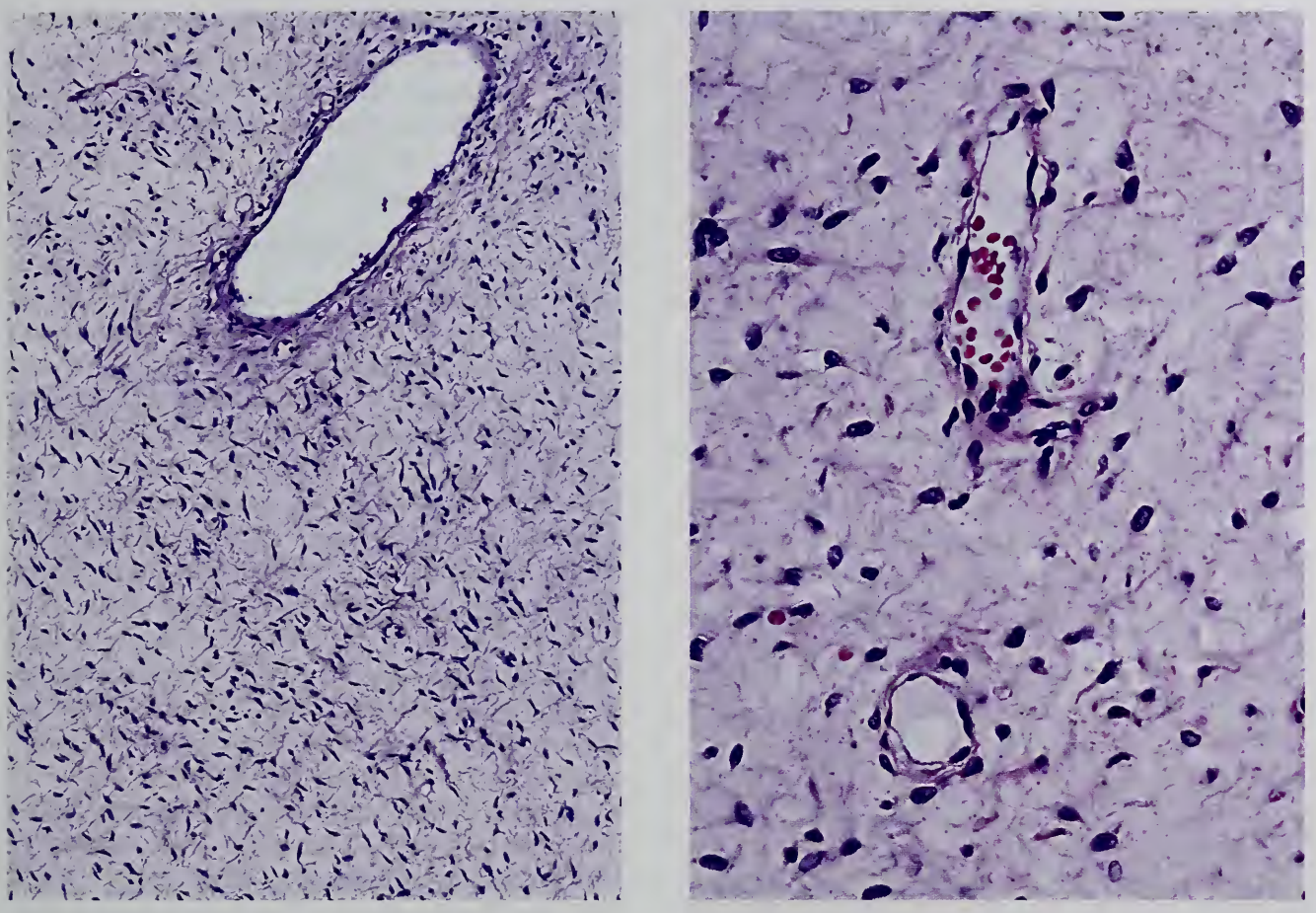


Figure 7-50

AGGRESSIVE ANGIOMYXOMA

Left: The tumor contains numerous nonarborizing blood vessels, consisting predominantly of capillaries and medium-sized arteries. The fibroblasts and myofibroblasts are spindle shaped to stellate, with small uniform nuclei containing dense chromatin and small nucleoli. No significant nuclear pleomorphism or atypia is present. Mitotic figures are rare. The tissue surrounding the cells appears myxoid in some areas and densely collagenous elsewhere.

Right: The tumor contains numerous nonarborizing blood vessels, consisting predominately of capillaries and arterioles. The cells have small uniform nuclei containing dense chromatin and small nucleoli. No significant nuclear atypia is present.

of both angiomyofibroblastoma and aggressive angiomyxoma have been described (147). The prominent small vessels and clustered muscular arteries distinguish aggressive angiomyxoma from intramuscular myxoma, fibromatosis, spindle cell lipoma, fibroepithelial polyp, and fibroepithelial stromal polyp with pseudosarcomatous features (308). Aggressive angiomyxoma entraps fat, but the absence of lipoblasts distinguishes it from myxoid liposarcoma. Neural elements may also be entrapped within the tumor, but the tumor lacks S-100 protein antigen, which is expected in a myxoid neurofibroma or schwannoma. Superficial angiomyxoma involves both the dermis and adjacent subcutaneous tissue. It is a superficial mass that typically does not involve deep tissues. Myxoid leiomyoma of the vulva may resemble angiomyxoma; immunohistochemical studies for smooth muscle markers distinguish these lesions (290).

The myxoid features of aggressive angiomyxoma may suggest myxoid malignant fibrous histiocytoma (MFH). Myxoid MFH may have a local infiltrative pattern similar to aggressive angiomyxoma. Myxoid MFH, however, has both acellular myxoid areas rich in mucopolysaccharides and more cellular areas composed of spindle-shaped cells arranged in a storiform pattern. In addition, myxoid MFH has multinucleated giant cells, pleomorphic giant tumor cells, histiocytic cells with foamy cytoplasm, and inflammatory cells consisting mainly of lymphocytes.

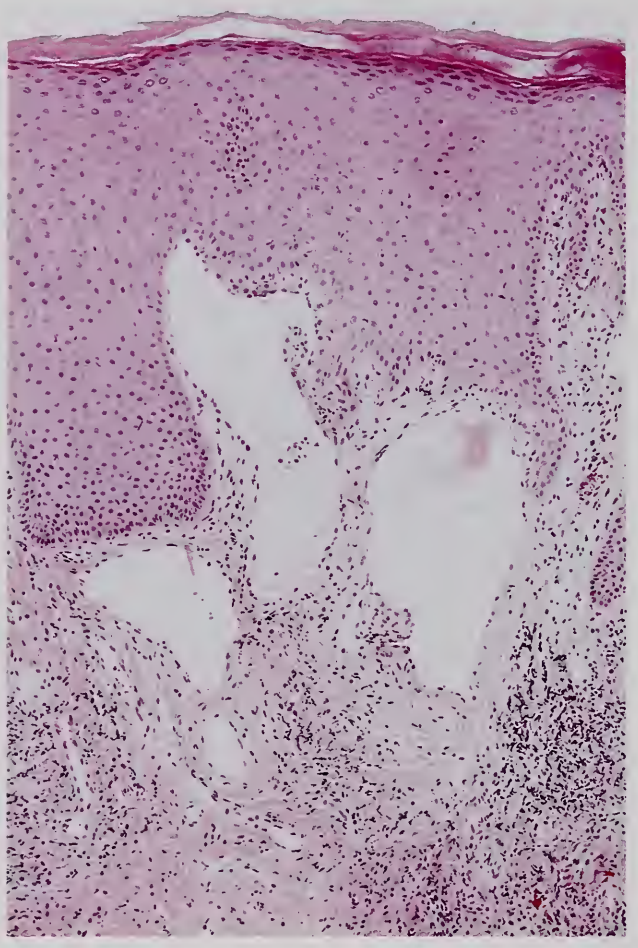


Figure 7-51

LYMPHANGIOMA

Lymphatic vessels of different sizes lie beneath and immediately adjacent to the overlying squamous epithelium.

Immunohistochemical studies are also of value in distinguishing these myxoid tumors.

Vulva hypertrophy with lymphedema may resemble aggressive angiomyxoma on diagnostic biopsy, although clinically, labial hypertrophy with lymphedema, unlike aggressive angiomyxoma, involves the vulva symmetrically. Individuals with such lymphedema may have a history of being disabled and bedridden or wheelchair bound. The changes are typically superficial, unlike angiomyxoma. Dilated and tortuous lymphatic channels, without pronounced, clustered thick-walled vessels also help distinguish lymphedema from angiomyxoma (438).

Primary treatment is wide local excision (partial deep vulvectomy) without lymphadenectomy. Local recurrence is observed in approximately half the reported cases, usually within 3 to 4 years after excision; however, recurrence has been described as late as 14 years postoperatively (113,300,304). Successful reexcision of recurrences has been reported.

Lymphangioma

Lymphangioma of the vulva is congenital or acquired and rare. When congenital it may be associated with lymphangiomas of the lower extremities. Congenital lymphangioma may be large and cavernous, with deep lymphatic involvement. Acquired vulvar lymphangioma may present as verrucous papules, rather than clustered small vesicles, and can resemble condyloma acuminatum (280). It may occur after pelvic radiation therapy, occurring in one case 15 years after radiation therapy for cervical carcinoma (381). Lymphangioma may also follow vulvar surgery, chronic infection, Crohn disease, or related congenital disorders such as dysplastic angiopathy and congenital lymphedema (280).

Lymphangioma is composed of variably sized endothelial-lined spaces that contain lymph and generally lack a muscular wall (fig. 7-51). Delicate fibrous connective tissue supports the endothelial-lined spaces. Hemangioma (see above) is the main lesion in the differential diagnosis of lymphangioma.

Surgical excision is applicable in selected cases, but no treatment is uniformly effective. Late local recurrence is common because of the difficulty of complete resection. Secondary infection is a serious complication.

Lymphangioma Circumscriptum

Lymphangioma circumscriptum presents in children or women of reproductive age. It is characterized by clusters of white to purple vesicles that are usually small; some vesicles, however, exceed 2 cm in diameter. The lesion clinically may resemble condyloma acuminatum (374).

A malformation or defect of dermal lymphatics is thought to be the basis of the lesion. Ulceration of the vesicles, with secondary infection and cellulitis, may be a complication.

Histopathologic features include subepithelial endothelial-lined cysts that are immediately adjacent to the basal layer, displacing the papillary dermis. Within the underlying reticular

dermis are dilated lymphatic spaces, some of which have prominent muscular walls. If deemed necessary, treatment is surgical excision or laser treatment (188,374).

Fibroma

Fibroma is a rare benign tumor of the vulva. It usually arises from the deeper fibrous tissue of the introitus, perineal body, or round ligament (185). The fibroma may enlarge the labium majus, be associated with dyspareunia, and clinically resemble an inguinal hernia (16). Although fibromas may become very large, they usually do not exceed 8 cm in diameter. Infarction or hemorrhage may be associated with pain and rapid enlargement of the tumor. The overlying skin is not attached to the fibroma and is usually similar in appearance to the adjacent vulvar skin. Malignant transformation is rare.

Histologic features include fibrocytes arranged in parallel and interlacing bundles. Cystic, hemorrhagic, hyaline, and myxomatous changes are observed. Some tumors contain fat tissue. The differential diagnosis includes a number of benign tumors and tumor-like lesions including fibroepithelial polyp, aggressive desmoid tumor, nodular fasciitis, leiomyoma dermatofibroma or fibrous histiocytoma, neurofibroma, schwannoma, and postoperative spindle cell nodule (107). Treatment is local excision.

Solitary Fibrous Tumor (Atypical Solitary Fibrous Tumor)

Benign *solitary fibrous tumor,* also termed *atypical solitary fibrous tumor,* is rare on the vulva. In one case, the tumor was 15 cm in greatest dimension and encapsulated. The tumor is yellow-white and lobulated on cut surface.

Solitary fibrous tumor has a variable microscopic appearance, with hypercellular areas and associated collagenous and myxoid stroma. The microscopic findings range from a cellular hemangiopericytoma-like appearance with prominent staghorn-shaped vessels in the central portion of the tumor, to areas with extensive perivascular and stromal hyalinization. Peripherally, the tumor has prominent small vessels, smaller stromal cells, and multinucleated giant cells. Fat tissue may be entrapped within the tumor. In the cellular areas, the tumor cell nuclei are hyperchromatic and oval to spindle shaped, and contain small nucleoli. Mild nuclear atypia is present (127,293). Necrosis may be present in the center of the lesion.

The tumor cells are immmunoreactive for vimentin, and some express CD34, bcl-2, and PR. They are negative for ER, desmin, S-100 protein, factor VIII, CD31, CAM 5.2, and EMA. Leu-7 and muscle-specific actin may be focally immunoreactive, although actins are usually negative. One tumor studied was DNA diploid (127).

Treatment is local excision. Malignant variants of this tumor have been described but not in the vulva (293).

Cellular Angiofibroma

Cellular angiofibroma is a rare benign tumor of the vulva occurring predominantly in middle-aged women (306). The tumor is typically under 3 cm in maximum dimension. Microscopically, cellular angiofibroma resembles angiomyofibroblastoma. The tumor is usually well circumscribed, but may focally infiltrate the adjacent dermis. It is composed predominately of small cribriform, spindle-shaped cells that are intermixed with mature-appearing adipocytes and delicate strands of collagen. The cells have a small amount of pale-staining cytoplasm and the nuclei are oval to fusiform in shape, without nuclear hyperchromasia. Significant nuclear pleomorphism is seen in some cases, and multinucleated tumor giant cells have been reported. Mitotic activity is variable but is usually under 5 mitotic figures per 10 high-power fields. Numerous blood vessels that are of small to medium size with hyalinized vessel walls are present. The tumor expresses vimentin and CD99, may express CD34, and is negative for S-100 protein, desmin, and actins, but immuohistochemistry is of limited value (85,298). DNA ploidy analysis performed in one case was diploid (85,298). Treatment is local excision (304,306).

Giant Cell Angiofibroma

Giant cell angiofibroma is a rare tumor of the vulva that is thought to overlap with solitary fibrous tumor. The tumor is within the soft tissue and is well circumscribed but not encapsulated. It contains both cellular and sclerosed areas, with some multinucleated stromal giant cells. The cellular areas consist of uniform spindled and round cells without significant cytologic atypia. Thick-

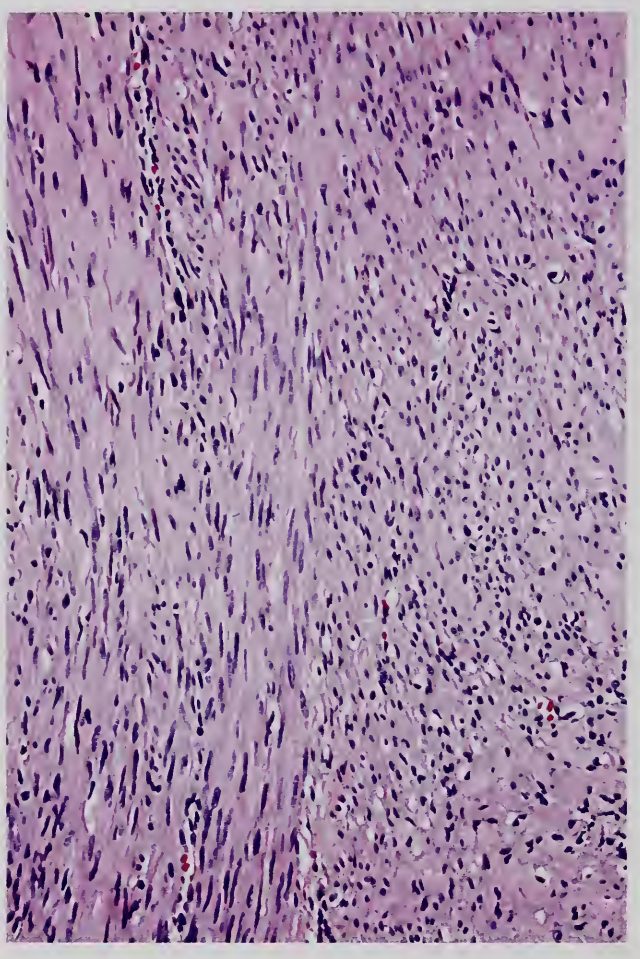


Figure 7-52

LEIOMYOMA

The tumor is composed of interlacing fascicles of uniform spindle-shaped smooth muscle cells with small regular nuclei.

walled vessels, which may be staghorn in shape, are present. Keloid type collagen is dispersed within the tumor. The mitotic count may be as high as 3 per 10 high-power fields (155).

Giant cell angiofibroma is immunoreactive for vimentin, CD34, and CD99. Focal reactivity for S-100 protein, smooth muscle actin, epithelial membrane antigen, keratin, and bcl-2 is also reported (155).

Leiomyoma/Atypical Leiomyoma

Leiomyoma is the most common soft tissue tumor of the vulva, although rare. The tumor has been described in childhood, where it may be related to esophagogastric leiomyomatosis, as well as in women up to 70 years of age or more. The median age is 41 years. Leiomyoma may arise from the smooth muscle of blood vessels, erectile tissue, and erector pili muscles. Leiomyoma of the vulva typically presents as a solitary mass and rarely exceeds 7 cm in diameter.

The tumor is composed of interlacing fascicles of smooth muscle (fig. 7-52). The smooth muscle cells have prominent eosinophilic cytoplasm with poorly defined cell borders. Clear cytoplasm is observed in some cases. The adjacent tissue may be hyalinized or myxoid, and mucin may be present. The nuclei are usually oval, with rounded rather than pointed poles.

Within the vulva, leiomyomas have a variety of morphologic types. Epithelioid and myxoid types have been found to be common in one review (295). Myxoid change has been observed with and without pregnancy (295). Most of these cases have adjacent areas of typical leiomyoma (295).

Leiomyomas are usually immunoreactive for vimentin, desmin, myosin, smooth muscle actin, and muscle-specific actin, and most express ER and PR. They do not express keratin or S-100 protein (295). Unlike rhabdomyoma they do not contain myoglobin.

Therapy for primary or recurrent vulvar leiomyoma is wide local excision because leiomyosarcoma cannot be excluded until multiple sections of the tumor are studied microscopically (see Leiomyosarcoma).

Atypical Leiomyoma. A leiomyoma is considered atypical if it has any one of the four findings that characterize a leiomyosarcoma: moderate to severe cellular atypia, a mitotic rate of 5 mitotic figures or more per 10 high-power fields, an infiltrative growth pattern, and size greater than 5 cm in greatest dimension. If any one of these features is present without other evidence of malignancy, such as metastasis or overt invasion, the tumor is classified as an *atypical leiomyoma* (295,298,304).

Granular Cell Tumor

Vulvar *granular cell tumor* comprises approximately 7 percent of all granular cell tumors. This is a tumor of peripheral nerve sheath origin that is usually benign, although 1 to 2 percent are malignant (396). Malignant vulvar granular cell tumor has been reported in a 17-year-old woman (346). In a study of 10 cases, the age range was 28 to 60 years, with a mean

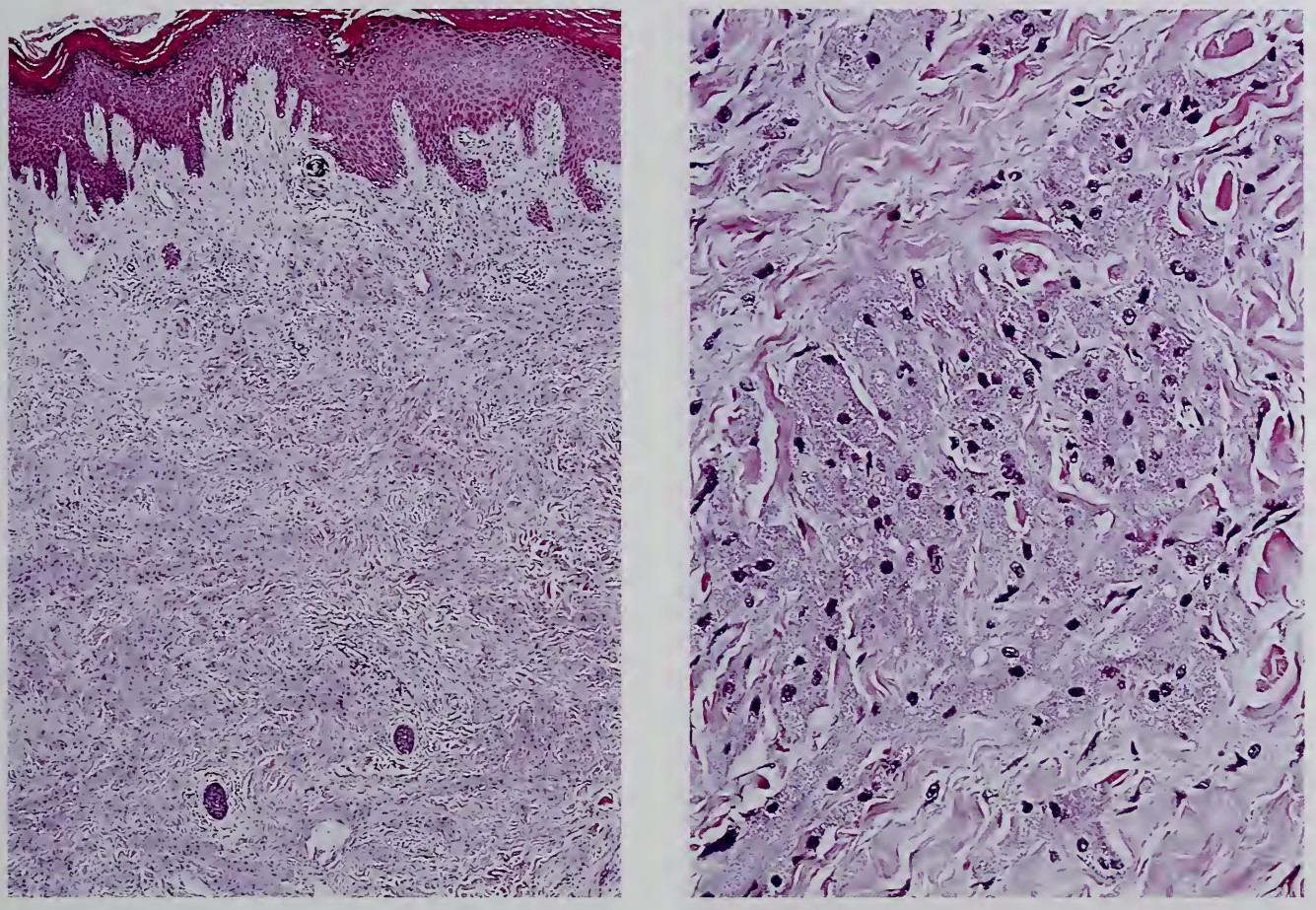


Figure 7-53

GRANULAR CELL TUMOR WITH PSEUDOCARCINOMATOUS HYPERPLASIA

Left: The overlying epithelium is hyperplastic and forms irregular nests with keratin pearls surrounded by the granular cell tumor, mimicking invasive squamous cell carcinoma. This pseudoepitheliomatous (pseudocarcinomatous) hyperplasia is related to the granular cell tumor that is within the underlying superficial dermis. The tumor has cells with abundant granular cytoplasm and small uniform nuclei. A delicate fibrovascular stroma separates groups of tumor cells.

Right: The tumor is within the superficial dermis and is composed of uniform cells with abundant cytoplasm and small uniform nuclei.

age of 39 (471); granular cell tumors also occur in children (41). The tumor is usually solitary, but multiple tumors are observed in 10 to 15 percent of cases (7,41,90,177,248,397).

The tumor presents as painless subcutaneous nodule that is typically under 3 cm in diameter. It may occur on the mons pubis, the labia majora, or clitoris. In the latter location it may mimic clitoral hypertrophy. Priapism of the crus of the clitoris has been reported secondary to a locally aggressive granular cell tumor (397).

Microscopic examination reveals a nonencapsulated mass with a pushing or infiltrative margin; perineural involvement may occur. The tumor cells are large and polyhedral, with abundant eosinophilic granular cytoplasm. The cell borders are indistinct and groups of cells are often separated by a small amount of hyalinized stroma (fig. 7-53). The nuclei are small and uniform. In up to half of the cases, the overlying epithelium exhibits pseudoepitheliomatous hyperplasia, which may resemble squamous cell carcinoma if the biopsy is not sufficiently deep to include the underlying granular cell tumor (fig. 7-53, right) (471).

Granular cell tumors are generally benign, although they can recur and metastasize. No unique morphologic features identify granular cell tumors with the risk of metastasis. In one study, tumors with pushing borders did not recur (7). The presence of an infiltrative pattern of growth may identify those tumors that have a

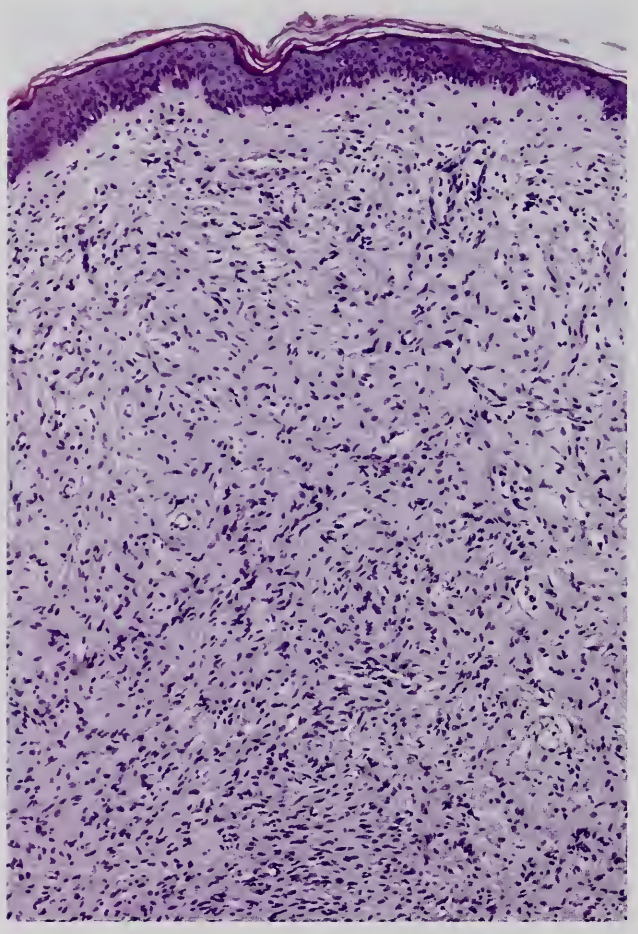


Figure 7-54

NEUROFIBROMA

The tumor is composed of intersecting bands of spindle cells, some of which have nuclei with pointed ends.

risk of recurrence, however, it is recognized that some tumors with benign pathologic features recur and behave in a malignant manner (396).

The cells of granular cell tumor are immunoreactive for S-100 protein antigen, myelin basic proteins PO and P2, lectin, and CEA. In one study, DNA aneuploidy was observed in a vulvar tumor with pulmonary metastasis; benign tumors were diploid (248).

The differential diagnosis includes superficially invasive squamous cell carcinoma and metastatic carcinoma if pseudoepitheliomatous hyperplasia is present. Xanthogranulomatous inflammation may resemble granular cell tumor. The feature most useful in distinguishing pseudoepitheliomatous hyperplasia from squamous cell carcinoma, either primary or metastatic, is severe cytologic atypia in the infiltrative squamous cells (471). The hyperplastic process may be as deep as 3 mm, however, it does not involve the underlying fat (298). Xanthogranulomatous inflammation differs in the more variable size of the histiocytes, an absence of prominent cytoplasmic granules, the presence of scattered inflammatory cells, and an absence of S-100 protein positivity.

The treatment of choice for granular cell tumors, primary and recurrent, is wide local excision.

Neurofibroma

Neurofibroma is a benign tumor of nerve sheath origin. It is solitary or multiple and associated with the inherited disorder, von Recklinghausen disease.

Nearly half of the neurofibromas arising within the vulva occur in women with von Recklinghausen neurofibromatosis (125). When associated with the disease, the tumors are polyclonal in origin; neurofibromas from normal individuals are monoclonal. Eighteen percent of women with neurofibromatosis have neurofibromas of the vulva. These painless tumors are rare before puberty, but grow rapidly thereafter. Growth at puberty may be related to the presence of ER and PR in the tumor. The tumors usually do not exceed 3 cm in diameter, but have been as large as 25 cm (402).

Neurofibromas are composed of spindle-shaped cells arranged in bundles that, when cut on the long axis, exhibit a distinctive wave-like whorled appearance. The cells have indistinct cell borders and may be associated with strands of collagen and mast cells (fig. 7-54). The nuclei are usually small and somewhat spindle shaped, with pointed ends. Occasionally, very large pleomorphic and hyperchromatic nuclei are encountered. This feature is referred to as "ancient change" and is not an indication of malignant transformation. Myxoid neurofibroma has a more hypocellular appearance, and has prominent mucin about the tumor cells.

Neurofibromas that involve the skin are not encapsulated and may infiltrate the dermis and underlying fat. The presence of even 1 mitotic figure per 10 high-power fields is considered sufficient evidence for the diagnosis of a neurofibrosarcoma.

The differential diagnosis includes aggressive angiomyxoma, malignant schwannoma, fibroma, and fibrous histiocytoma. Aggressive

angiomyxomas have clustered muscular arteries within a myxoid stroma and are poorly circumscribed. Malignant schwannomas are highly cellular with a high mitotic count. In addition, nuclear palisading is distinctive and heterologous elements may be found. Neurofibromas are immunoreactive for S-100 protein antigen whereas fibromas lack such immunoreactivity, as do fibrous histiocytomas, which are rich in alpha-1-antichymotrypsin.

Small vulvar neurofibromas associated with neurofibromatosis do not require treatment. Enlarging or symptomatic tumors are excised. Although neurofibromas are benign, malignant transformation occasionally occurs in patients with von Recklinghausen disease (125).

Schwannoma (Neurilemmoma)

Schwannoma, also termed *neurilemmoma,* of the vulva is usually solitary and encapsulated, and may involve the clitoris, mimicking clitoral hypertrophy or Bartholin gland abscess (164, 178,239). Plexiform schwannoma has been described in the labia of a 5-year-old girl (377).

Microscopically, schwannomas characteristically exhibit both cellular and hypocellular areas. The cellular (Antoni type A) areas contain spindle cells with elongated or oval nuclei that are palisaded (fig. 7-55). Mitotic figures are usually rare, but may be observed in low numbers within the cellular areas. The cytoplasm is fibrillar with poorly defined cell borders. Verocay bodies are common in these areas and form as a result of alignment of the nuclei in rows separated by acellular zones.

The hypocellular (Antoni type B) areas contain spindle cells, small cells with hyperchromatic nuclei, and histiocytes filled with lipid vacuoles. Collagen fibers and mast cells are common. The hypocellular areas are typically myxomatous and occasionally cystic.

Schwannomas must be differentiated from leiomyomas. Schwannomas contain S-100 protein, like neurofibromas, and lack the desmin and smooth muscle actin seen in leiomyoma (see Malignant Schwannoma).

Paraganglioma

Paraganglioma has been described as a primary tumor of the vulva (75). The tumor is composed of nests of cuboidal-shaped neuroendocrine cells ("zellballen") with granular cytoplasm in fibrovascular tissue. Some nuclear pleomorphism may be present, and mitotic figures are rare. A reticulin stain demonstrates the nonstaining neuroendocrine cells surrounded by the reticulin-rich fibrovascular stroma.

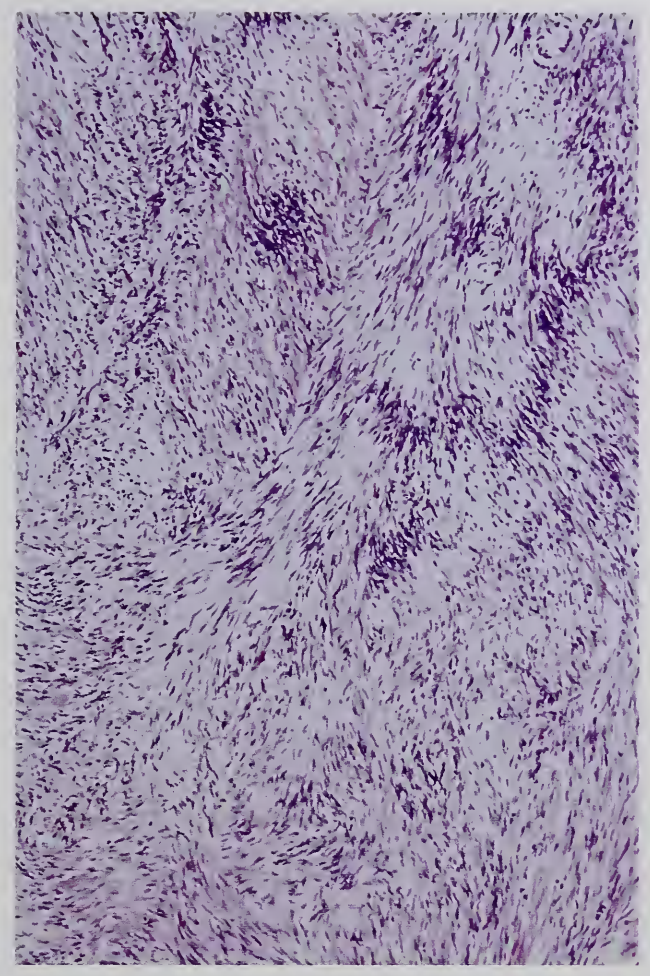


Figure 7-55

SCHWANNOMA, BENIGN (NEURILEMOMA)

The spindle cells are arranged in palisades.

Glomus Tumor

The *glomus tumor* presents as a painful solitary tumor, usually less than 4 cm in diameter. It may cause severe introital dyspareunia, with the pain characteristically localized to the tumor nodule. Glomus tumors are composed of epithelioid-appearing cells, which are of smooth muscle or pericyte origin, arranged in lobules about vascular channels. The surrounding hyalinized stroma contains mast cells as well as identifiable nerve elements (199,212).

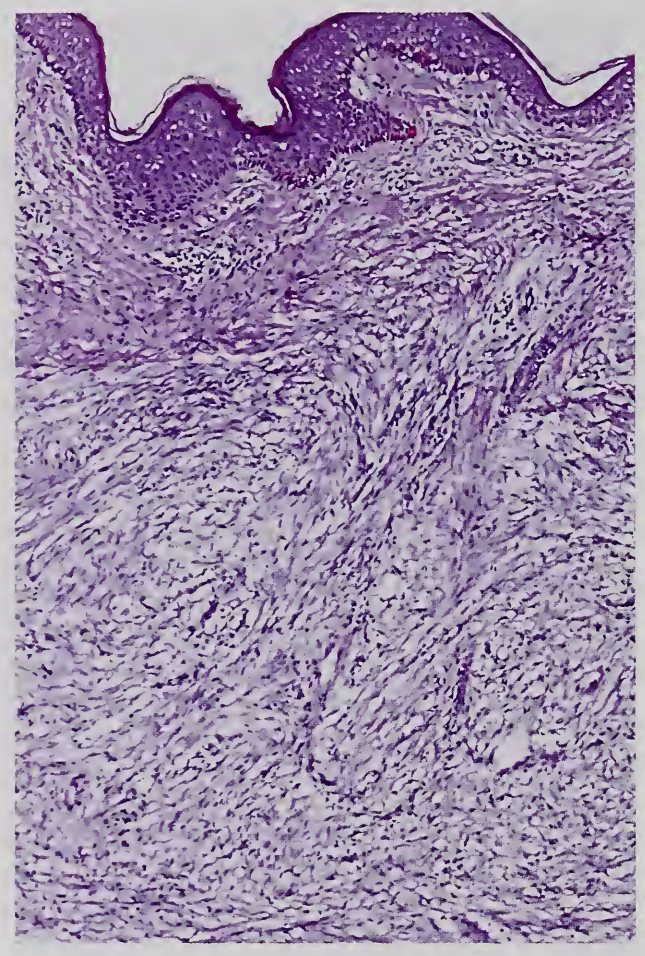


Figure 7-56

BENIGN FIBROUS HISTIOCYTOMA

This tumor is composed of uniform-shaped cells and blends into the adjacent dermis. The tumor is located immediately below the epithelium, separated from the overlying epithelium by a thin band of dermis, and confined to the dermis.

Benign Fibrous Histiocytoma

Benign fibrous histiocytoma is a benign tumor of fibrohistiocytic origin. It is also referred to as *dermatofibroma, subepidermal nodular fibrosis, histiocytoma*, or *sclerosing hemangioma*, but the term benign fibrous histiocytoma is preferred. This neoplasm is rare on the vulva and presents as a solitary pigmented subcutaneous nodule.

Microscopically, the cells are arranged in a distinctive storiform pattern. Variable degrees of cellularity and collagenization occur (fig. 7-56). Mitotic activity is low or absent. Histiocytes, lymphocytes, and giant cells may be seen. This tumor is immunoreactive for stromelysin 3, alpha-1-antichymotrypsin and alpha-1-antitrypsin (82,238), vimentin, and factor XIIIa, and may be focally immunoreactive for smooth muscle actin and CD34. Dermatofibrosarcoma protuberans, which is included in the differential diagnosis, is negative for factor XIIIa and stromelysin 3, and immunoreactive for CD34 (82).

Atypical Fibrous Histiocytoma

Atypical fibrous histiocytoma has been documented in the vulva. The atypical features include nuclear atypia in the multinucleated giant cells, increased mitoses, and atypical mitotic figures. Size exceeding 2 cm, necrosis within the tumor, and involvement of the adjacent superficial subcutis may also be observed. Recurrence is local. Metastasis was observed in 2 of 59 cutaneous lesions in one series (197).

Rhabdomyoma

Rhabdomyoma is a benign tumor of striated muscle origin. It has been reported in women of reproductive age (470). Rhabdomyoma is usually polypoid and unencapsulated, and is composed of mature striated muscle cells with fibrovascular tissue. There is a fetal myxoid variant of this tumor. Rhabdomyoma is not infiltrative and lacks nuclear atypia and mitotic activity, features that assist in distinguishing it from rhabdomyosarcoma.

MALIGNANT MESENCHYMAL TUMORS

As with benign mesenchymal tumors, most *malignant mesenchymal tumors* involving the vulva occur more frequently at other sites. A brief discussion of these tumors follows; for a more complete discussion, the reader is referred to the referenced articles or to a comprehensive reference on soft tissue tumors.

Rhabdomyosarcoma

Rhabdomyosarcoma is a malignant soft tissue neoplasm exhibiting features of striated muscle. It is the most common sarcoma of soft tissue in infants and children. Although most patients are under 10 years of age, some are in early adolescence to approximately 20 years of age, and occasionally older (451). It is a rare tumor in the vulva. The Armed Forces Institute of Pathology (AFIP) reported the vulva or vagina as the primary site of the tumor in under 1 percent (5 cases) of 558 cases (451). Of 38 patients

with nonmetastatic rhabdomyosarcoma of the genital tract, 4 had primary vulvar tumors, 23 had primary vaginal tumors, and 11 had uterine or cervical tumors (257). In this study, the mean age at diagnosis of vulvar or vaginal rhabdomyosarcoma was 21 months (9 months to 15.6 years) and 15 months for uterine-cervical tumors (10 months to 16.6 years), reflecting the earlier age presentation for vulvar and vaginal tumors (257). Presenting symptoms include a vulvar mass and bleeding due to ulceration (410). Rhabdomyosarcoma of the vagina may secondarily involve the vulvar vestibule and labia, in which case the tumor is classified and staged as vaginal in origin.

The Pediatric Intergroup Rhabdomyosarcoma study classification of rhabdomyosarcoma classifies these tumors into four microscopic groups based on clinical behavior (300). Botryoid and spindle cell rhabdomyosarcomas are classified as of superior prognosis, embryonal rhabdomyosarcoma without distinguishing features is classified as of intermediate prognosis, alveolar and undifferentiated tumors are classified as of poor prognosis, and rhabdomyosarcoma with rhabdoid features is classified as not evaluable as to prognosis. In reporting the frequency of rhabdomyosarcoma, the vulva and vagina are usually combined as one site in large series, limiting specific statistics on vulvar tumors (301,451).

Although the evidence is limited in regard to the frequency of histologic subtypes of rhabdomyosarcoma of the vulva, botryoid, alveolar, and embryonal tumors (without other distinguishing features) are the predominate histologic types. Spindle cell and undifferentiated rhabdomyosarcomas occur predominately in men, and are rare in the vulva (80,348). These subtypes are distinguished by microscopy; cytogenetic studies are of value in identifying the alveolar subtype. The histologic type influences prognosis (32,257,264).

Botryoid Rhabdomyosarcoma

Botryoid rhabdomyosarcoma of the vulva typically involves mucosal sites. It is a firm submucosal or polypoid mass that simulates a bunch of grapes (hence the term *sarcoma botryoides*). In the vulva, the tumor arises from the labial or perineal area, and rarely from the clitoris (32). Although most cases of rhabdomyosarcoma present by 10 years of age, the majority of botryoid cases present in children under 2 years of age (see chapter 6) (78).

Botryoid rhabdomyosarcoma is usually polypoid when it is superficial and associated with the mucosa of the labia or vestibule. The polypoid features are not necessary for a diagnosis, but the characteristic cambium layer is the microscopic key feature. A thin epithelial surface, beneath which is a narrow, but richly cellular, subepithelial (cambium) layer of tumor cells, overlies an edematous or myxoid hypocellular zone (fig. 7-57). The tumor cells may invade the overlying epithelium singly or in small groups. The myxoid areas may contain small, round to spindle-shaped cells with small nuclei that lack nuclear atypia. Cystic degeneration may occur within the myxoid areas, resulting in a microcystic appearance.

The cellular area of the tumor ranges from undifferentiated spindle-shaped cells with small nuclei and dense chromatin to cellular areas with round to spindle-shaped rhabdomyoblasts with prominent, dense, eosinophilic cytoplasm and large, pleomorphic, and hyperchromatic nuclei. The rhabdomyoblasts, when present, may be grouped and associated with a prominent foamy histiocytic infiltrate that can obscure the typical histopathologic features. Hematoxylin and eosin (H&E) stains the cross striations of the tumor cells in less than 25 percent of cases. Mitotic figures are usually readily identified.

The cytoplasm of most tumor cells are immunoreactive for muscle-specific actin (HHF-35) and desmin. Troponin-T and sarcomeric actin are less frequently immunoreactive, and smooth muscle actin is often negative (451). Myogenin and MyoD1 may be of value in differentiating rhabdomyosarcoma from other sarcomas (451). Although myogenin and myoglobin are specific for skeletal muscle, they are not always demonstrable in rhabdomyosarcoma; myoglobin is immunoreactive in less than half of the cases. Electron microscopy is not necessary for a diagnosis (278).

The tumor invades locally, with late metastases to regional lymph nodes, lungs, and distant sites. Tumor cells were reported in the peripheral blood smear (carcinocythemia) of a patient with advanced of rhabdomyosarcoma (249).

The prognosis is dependent upon the clinical stage, size, and histologic type of the tumor

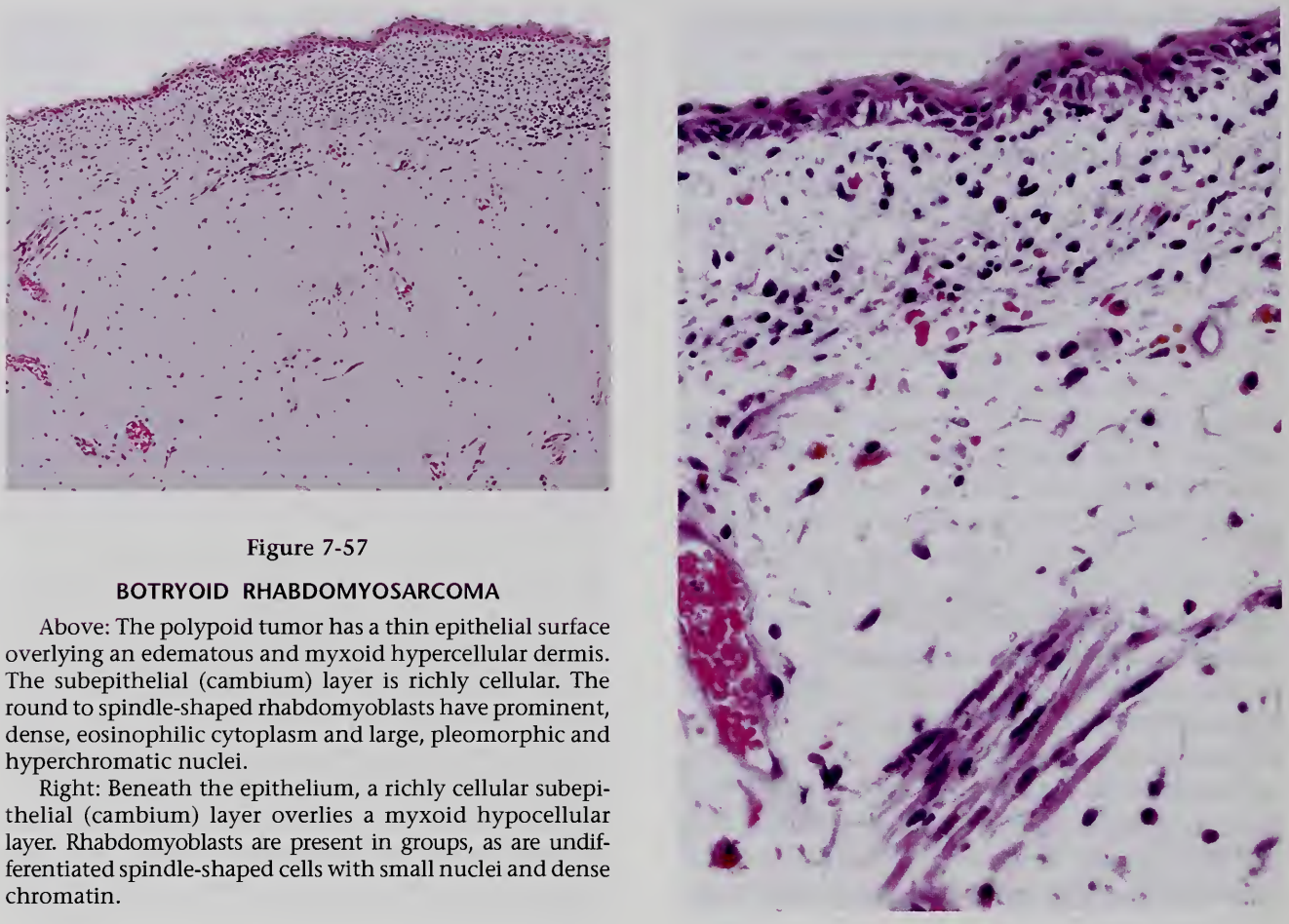


Figure 7-57

BOTRYOID RHABDOMYOSARCOMA

Above: The polypoid tumor has a thin epithelial surface overlying an edematous and myxoid hypercellular dermis. The subepithelial (cambium) layer is richly cellular. The round to spindle-shaped rhabdomyoblasts have prominent, dense, eosinophilic cytoplasm and large, pleomorphic and hyperchromatic nuclei.

Right: Beneath the epithelium, a richly cellular subepithelial (cambium) layer overlies a myxoid hypocellular layer. Rhabdomyoblasts are present in groups, as are undifferentiated spindle-shaped cells with small nuclei and dense chromatin.

(348). Patients with tumors under 5 cm in greatest dimension have a better prognosis than those with larger tumors and the prognosis is most favorable when the tumor can be completely excised. Histologic type is related to prognosis: botryoid rhabdomyosarcoma is associated with an excellent prognosis, with the 5-year survival rate exceeding 90 percent; embryonal rhabdomyosarcoma without distinguishing features is associated with an intermediate prognosis; alveolar rhabdomyosarcoma is associated with a more guarded prognosis (78,80,264,451).

Recent therapeutic approaches have employed chemotherapy, including actinomycin D, ifosfamide (or cyclophosphamide), etoposide, and vincristine (264). Conservative surgery may be needed to excise the tumor. Radiation therapy is effective in some cases, and fertility can be preserved (257,264). The overall 5-year survival rate ranges from 85 to 97 percent; patients with small, localized tumors have the best prognosis (257,264)

Alveolar Rhabdomyosarcoma

Cutaneous *alveolar rhabdomyosarcoma* is less common than embryonal rhabdomyosarcoma when perineal, vaginal, and vulvar cases are included in the analysis. This type accounts for approximately 15 percent of rhabdomyosarcomas in the perineal area (80,103,142,181,318,391). In one study, 56 percent of rhabdomyosarcomas arising in the perineum of patients under 21 years of age were alveolar and 21 percent were embryonal (348).

Alveolar rhabdomyosarcoma is well documented as a primary vulvar tumor, and is reported predominantly in children under 7 years of age. The tumor may be congenital and has been described in a 7-month-old who had symmetric enlargement of the labia majora, minora, and clitoris resulting in an ambiguous appearance of the external genitalia (142). This case also demonstrated the red to blue "blueberry muffin" appearance of the involved skin that is

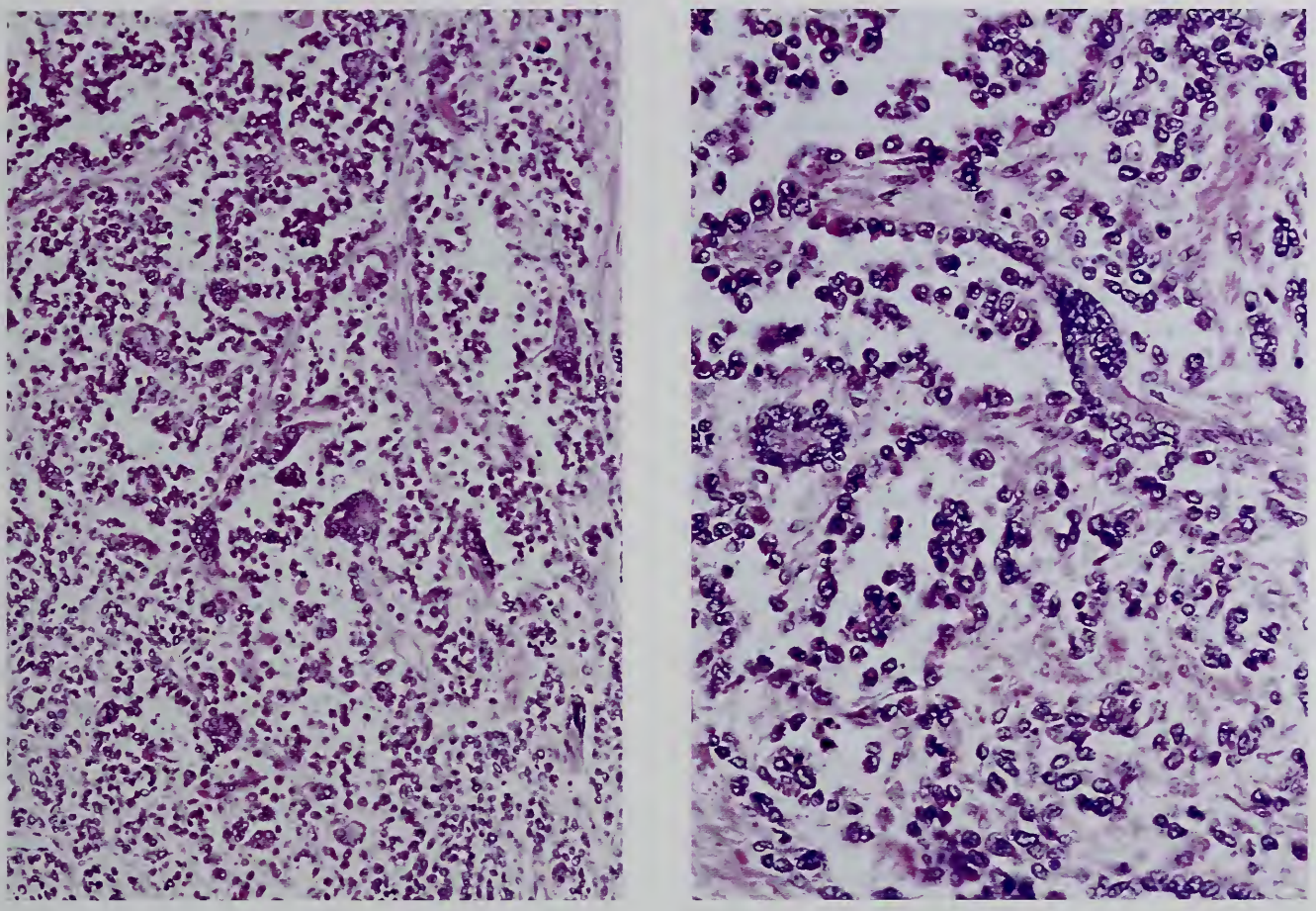


Figure 7-58

ALVEOLAR RHABDOMYOSARCOMA

Left: The tumor involves the deep dermis and is composed of round to spindle-shaped cells with scant cytoplasm. The cystic spaces, lined by tumor cells supported by fibrovascular septa, with associated hypocellular edematous stroma, give an alveolar-like appearance to the tumor. Mitotic figures are common.

Right: The cystic spaces are lined by round cells with scanty cytoplasm. Associated multinucleated tumor giant cells, with nuclei arranged in a "wreath-like" manner, are present. (Left and right courtesy of Dr. John Reith, Gainesville, FL.)

associated with these tumors. Clinically, the vulvar enlargement is a subcutaneous mass that may resemble a Bartholin cyst or perianal abscess.

The tumor is composed of round to spindle-shaped cells with scant cytoplasm (fig. 7-58). Typical "strap" cells with cross striations and rhabdomyoblasts may be seen more centrally and deeper. The cutaneous type alveolar rhabdomyosarcoma is found from the papillary to the deeper dermis, and may involve adjacent subcutaneous fat. Mitotic figures are common. Vascular spaces may be involved by tumor. Cystic spaces lined by tumor cells and supported by fibrovascular septa, with associated hypocellular edematous stroma, give an alveolar-like appearance to the tumor. In approximately 10 percent of tumors, the alveolar pattern is only focal, surrounded by tumor with an embryonal and/or solid pattern of growth (292). The alveolar-like spaces may be small, giving a microalveolar appearance that resembles the glands of adenocarcinoma (292).

The tumor cells are usually round and pleomorphic, with eosinophilic cytoplasm that appears denser about the nucleus. The nuclei are round to oval with radial dispersion of nuclear chromatin, giving the nuclear membrane an irregular appearance. The chromatin is generally coarse and nucleoli, when present, are usually small. Associated multinucleated giant cells, with nuclei having a "wreath-like" appearance, may be present. The typical strap cells of rhabdomyosarcoma may not be identified. The tumor may be diagnosed by cytologic

examination of fine needle aspiration samples (181). Immunohistochemical findings are as described for botryoid rhabdomyosarcoma and are dependent somewhat on the degree of tumor differentiation (318).

Over half of alveolar rhabdomyosarcomas have a t(2;13)(q35;q14) translocation, with about one-fifth having t(1;13)(p36;q14) (264, 318). Approximately three fourths of the cases express the fusion transcript *PAX3-FKHR* or *PAX7-FKHR,* which is related to translocations located on chromosomes 2 (*PAX3*) and 1 (*PAX7*) (264,318,451). These specific molecular markers or chromosome abnormalities are specific for alveolar rhabdomyosarcoma, and not associated with the embryonal type (264).

Treatment is dependent upon tumor size and stage, and influenced by response to first-line chemotherapy. Alveolar rhabdomyosarcoma is generally associated with a worse prognosis than the embryonal type.

Embryonal Rhabdomyosarcoma

Embryonal rhabdomyosarcoma usually presents as a subcutaneous or deep-seated mass. On gross examination the mass is not encapsulated, and has margins that are infiltrative. The tumor is typically nodular, with a white to gray to pink color. Areas of cystic and hemorrhagic change are often present.

Embryonal rhabdomyosarcoma is a cellular tumor with intermixed, and often contiguous, myxoid areas that may be associated with cystic change and hemorrhage. The cell population varies from poorly differentiated, small spindle-shaped cells with nuclear hyperchromasia, to larger cells that are round to oval to spindle shaped and have prominent eosinophilic cytoplasm, eccentric nuclei, and nuclear hyperchromasia. Cross striations are present in the spindle-shaped cells in half of the cases (300, 451). Immunohistochemical findings are as described for botryoid rhabdomyosarcoma, and are dependent somewhat on the degree of tumor differentiation (318).

These tumors usually have allelic loss in chromosome region 11p15. They may also have chromosomal alterations, including increased chromosomal numbers specifically related to chromosomes 13, 8, and 2, such as trisomy 8 (264,318,451).

Treatment is dependent upon tumor size and stage, and influenced by the response to first-line chemotherapy. Embryonal rhabdomyosarcoma is associated with a worse prognosis than the botryoid type.

Alveolar Soft-Part Sarcoma

Alveolar soft-part sarcoma is rare in the vulva; it occurs more commonly in the corpus, cervix, and vagina (294). It has been reported as a primary tumor arising in the labia minora, and as a tumor symmetrically enlarging the labia majora, labia minora, and clitoris (391).

The tumor usually has a pushing border and is composed of loosely arranged groups of epithelial-like cells with prominent granular eosinophilic cytoplasm that are arranged in an alveolar-like pattern. The tumor cells have uniform, large, round nuclei with prominent nucleoli and only rare mitotic figures. The tumor cells are supported on fibrovascular and fibrocollagenous stalks of varied thickness. Although an alveolar pattern is usually present, glands or secretory products are not seen (391).

Within the cytoplasm, highly characteristic groups of PAS-positive, diastase-resistant, rod-shaped crystalline structures are found in some cases. Electron microscopy demonstrates membrane-bound crystals or granules in most cases (294). Expression of muscle-related antigens, including MyoD1, supports the cell of origin of alveolar soft-part sarcoma as striated muscle cells (13,281,366).

Immunohistochemical studies are not of great value in establishing the diagnosis. Occasional immunoreactivity for S-100 protein and HMB45 and the presence of melanin may be misleading. Electron microscopy is helpful in equivocal cases (294).

The differential diagnosis includes metastatic renal cell carcinoma, clear cell tumor, melanoma, metastatic adenocarcinoma, and paraganglioma (238). Local recurrence is seen in approximately one third of the cases; regional or distant lymph node metastasis also occurs. The reported 5-year survival rate in patients with nonvulvar tumors is 60 percent (294,391). Therapy is partial deep vulvectomy with ipsilateral inguinal-femoral lymphadenectomy. Postoperative chemotherapy or immunotherapy may be of value (391).

Leiomyosarcoma

Leiomyosarcoma is the most common sarcoma of the vulva. It occurs predominantly in women of reproductive age, with a mean age of 38 years in one series (295). It occurs in postmenopausal women and has also been reported in adolescents (87,295,300,412,413). The tumor arises in the labium majus, the Bartholin gland area, the clitoris, and the labium minus in decreasing order of frequency. Usually 5 cm in diameter or larger when diagnosed, leiomyosarcoma generally does not exceed 10 cm. The clinical manifestations include pain and rapid growth.

The tumor is circumscribed or infiltrative. Most are of the spindle cell type, composed of interlacing bundles of spindle-shaped cells with eosinophilic cytoplasm (fig. 7-59). When the cells are sectioned at right angles to their long axis, a perinuclear halo is seen. The tumor may be predominantly epithelioid, or mixed with epithelioid and spindle cells. Myxoid and hyaline changes may be observed.

Leiomyosarcomas may have mitotic counts exceeding 10 per 10 high-power fields (87). In one series of 25 cases, the mitotic rate averaged 1.8 per 10 high-power fields (295). Severe cytologic atypia is seen in approximately 25 percent of the cases, with the remainder having moderate or mild atypia.

The proposed criteria for establishing a diagnosis of leiomyosarcoma include the evaluation of four specific features: a maximum dimension of 5 cm or larger, infiltrative margins, moderate to severe cytologic atypia, and a mitotic figure count of 5 or more per 10 high-power fields (295). Tumors with three or more features can be classified as leiomyosarcoma using these expanded criteria (295). A tumor with one or two of these findings, without other evidence of malignancy, such as metastasis or overt invasion, is classified as an *atypical leiomyoma* (87,295,412). Smooth muscle tumors with infiltrative borders that have a mitotic rate exceeding 5 per 10 high-power fields have a higher rate of recurrence than tumors that are well circumscribed. Neoplasms that are 5 cm or greater in diameter also have a higher rate of recurrence than those less than 5 cm in diameter (87). *Myxoid leiomyosarcoma* and *epithelioid leiomyosarcoma* are vulvar variants of leiomyosarcoma (412).

The immunohistochemical findings are the same as those for leiomyomas, with the tumor cells usually expressing vimentin, smooth muscle actin, and ER and PR. The tumor may also express androgen receptor (AR) (242). Markers for cell proliferation, such as MIB-1 (Ki-67), have been used to determine cell proliferation but their prognostic value as compared to the mitotic count is still a matter of study.

Wide local excision (partial deep vulvectomy) or total deep vulvectomy is the initial treatment of choice if the tumor is confined to the vulva (12a). Radiation therapy to the tumor field may be used preoperatively or postoperatively in these cases, however, there is very limited experience with this approach. Leiomyosarcoma of the vulva tends to recur locally; however, pulmonary, hepatic, and other distant metastases also occur (12a,295). Regional lymph node metastasis is uncommon (295).

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a malignant cutaneous soft tissue tumor that is rare in the vulva. It occurs predominately in postmenopausal women of a median age of 54 years. The tumor presents as a firm subcutaneous nodular mass that averages 5 cm in greatest dimension. The overlying skin may be pigmented, resembling a nevus (136,300,382). The tumor is usually slow growing but may grow rapidly during pregnancy. Satellite nodules and metastasis occur in advanced cases.

Dermatofibrosarcoma protuberans diffusely infiltrates the dermis, especially in the deeper areas, and may invade the epidermis with resultant ulceration (238), as well as the subcutaneous fat. Satellite nodules may be present. The fibroblast-like cells composing the tumor are arranged in a distinctive storiform pattern, which is most readily apparent near the central portion of the tumor. Peripherally, the cells appear bland and uniform, but centrally, nuclear pleomorphism, atypia, and occasional mitotic figures may be evident (fig. 7-60). Tumor giant cells, marked nuclear pleomorphism, and many mitotic figures are typically not seen, which helps distinguish this tumor from malignant fibrous histiocytoma. There is strong immunoreactivity for CD34 in most tumors, and, in contrast to dermatofibroma, negativity for stromelysin 3 (82,136).

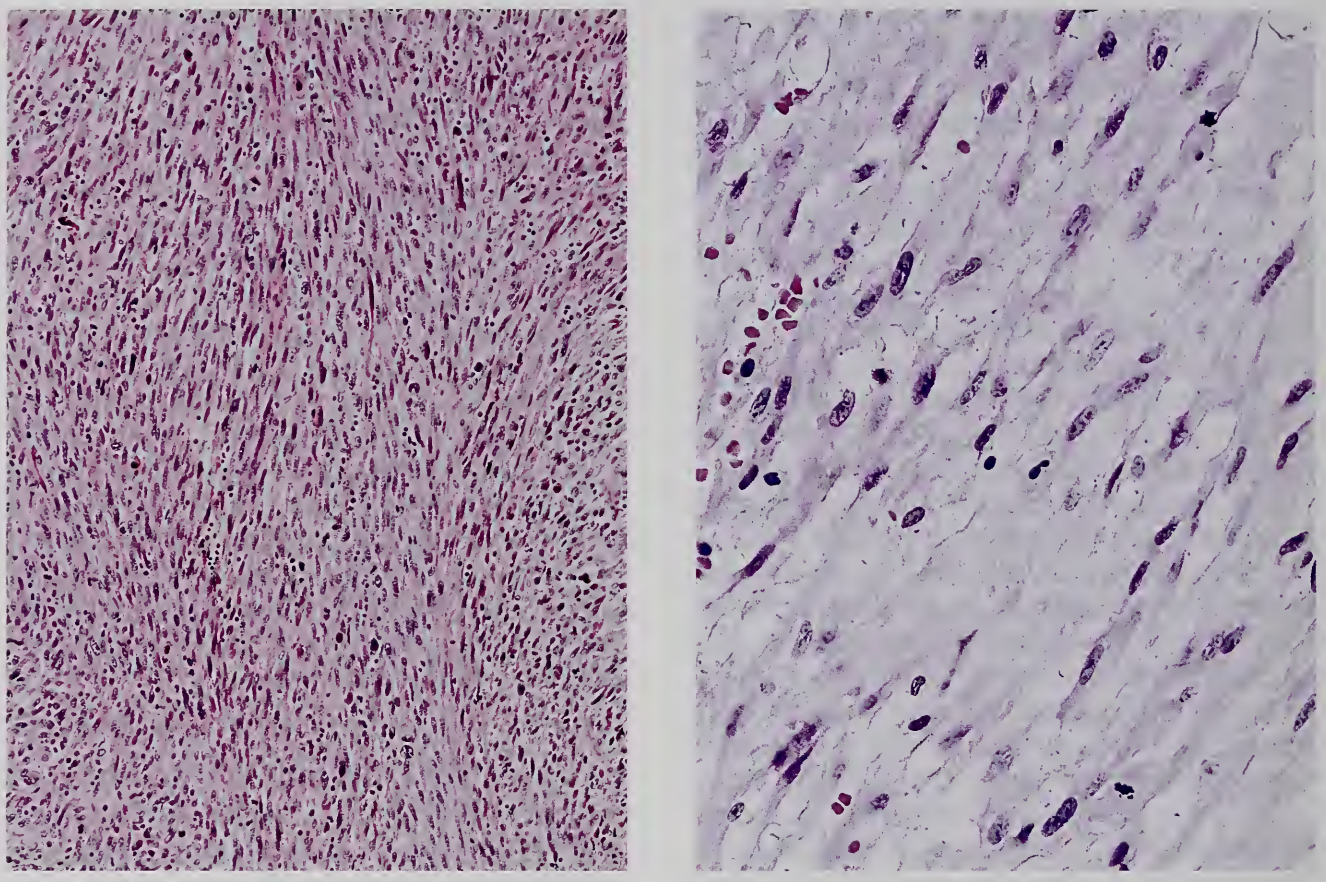


Figure 7-59

LEIOMYOSARCOMA

Left: The cells are spindle shaped with oval nuclei and myxoid cytoplasm. There were 13 mitotic figures per 10 high-power fields.

Right: The tumor is composed of spindle-shaped smooth muscle cells with some nuclear atypia. Two mitotic figures are present in this field and up to 5 per 10 high-power fields were identified.

Wide local excision (partial vulvectomy) is the treatment of choice and the survival rate is 91 to 100 percent. Local and regional recurrence is common (20 to 49 percent of cases) (276). Distant lymph node involvement and pulmonary metastasis are infrequent (399). Recurrent tumor may dedifferentiate into fibrosarcoma, which also expresses CD34 (136).

Composite Tumor Consisting of Dermatofibrosarcoma Protuberans and Giant Cell Fibroblastoma

Composite tumor consisting of dermatofibrosarcoma protuberans and giant cell fibroblastoma is a rare tumor reported in the vulva of women of reproductive age. In one case, the tumor was associated with a vulvar endometrioma (207). The tumor presents as a subcutaneous mass that microscopically consists of dermatofibrosarcoma protuberans and giant cell fibroblastoma. In one case, the tumor contained a *COL1A1/PDGFB* fusion point as has been reported in giant cell fibroblastoma, suggesting a relationship between these two tumors (441).

Malignant Fibrous Histiocytoma

Malignant fibrous histiocytoma (MFA) is a malignant neoplasm of histiocytes that has undergone fibroblastic differentiation. Although rare in the vulva, MFH is the second most common sarcoma at this site (87). In the vulva it most commonly presents as a large solitary mass in middle-aged women (300,415).

MFH is typically a deep tumor and may be attached to the deep fascia. It is solid and white to yellow on sectioning. Areas of necrosis and hemorrhage may be seen. The tumor usually infiltrates adjacent tissue.

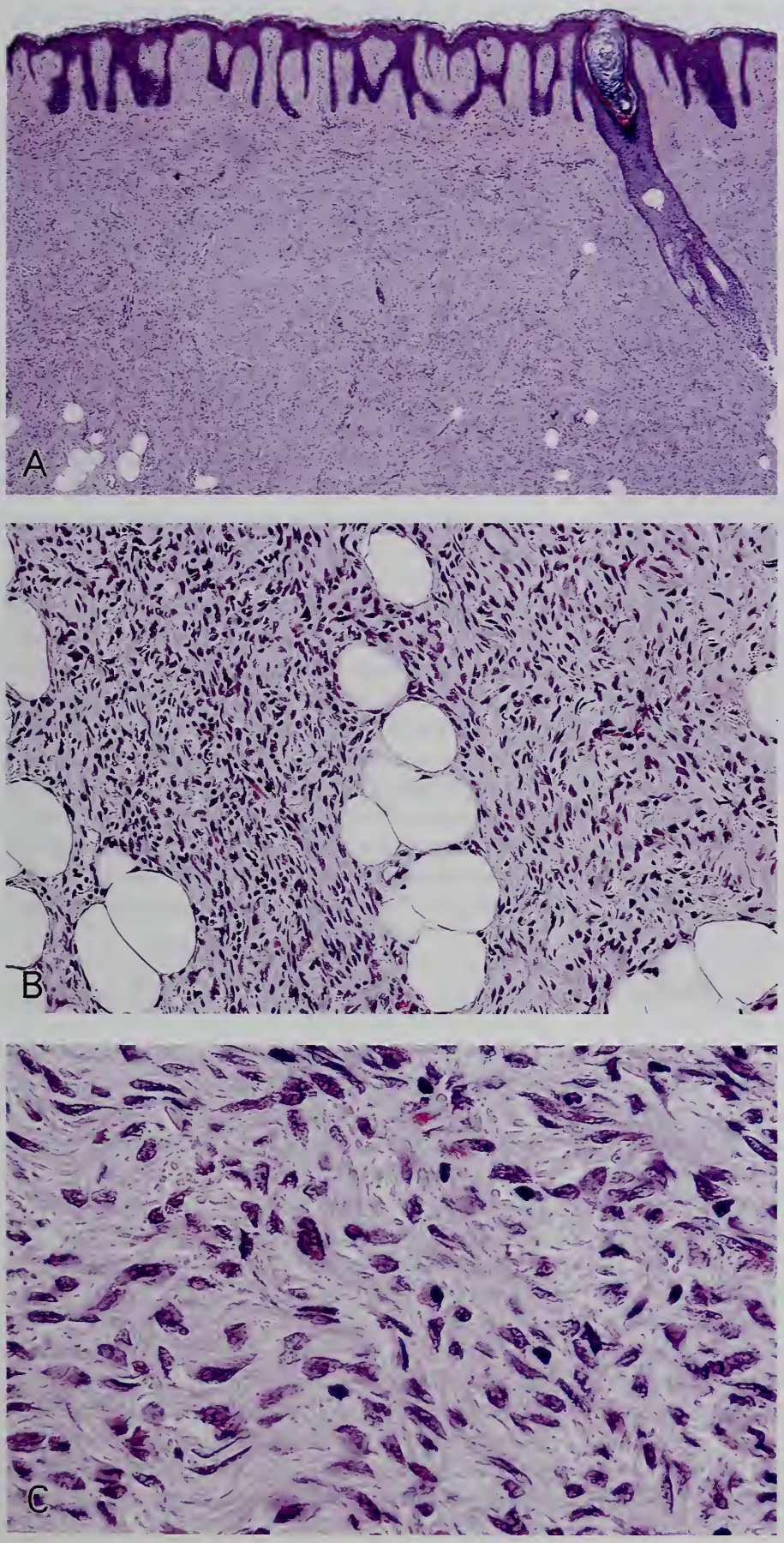


Figure 7-60

DERMATOFIBROSARCOMA PROTUBERANS

A: The overlying hyperkeratotic epithelium is thin, with a superficial dermal edematous zone adjacent to the underlying tumor. The tumor cells are arranged in a storiform pattern and are pleomorphic, with some multinucleation. The nuclei are large and the cytoplasm is pale.

B: The pleomorphic tumor cells have eosinophilic cytoplasm. Fat is trapped within the invasive tumor.

C: The tumor cells are spindled-shaped to round, with nuclear atypia. (Courtesy of Dr. Bridgett Ronnett, Baltimore, MD.)

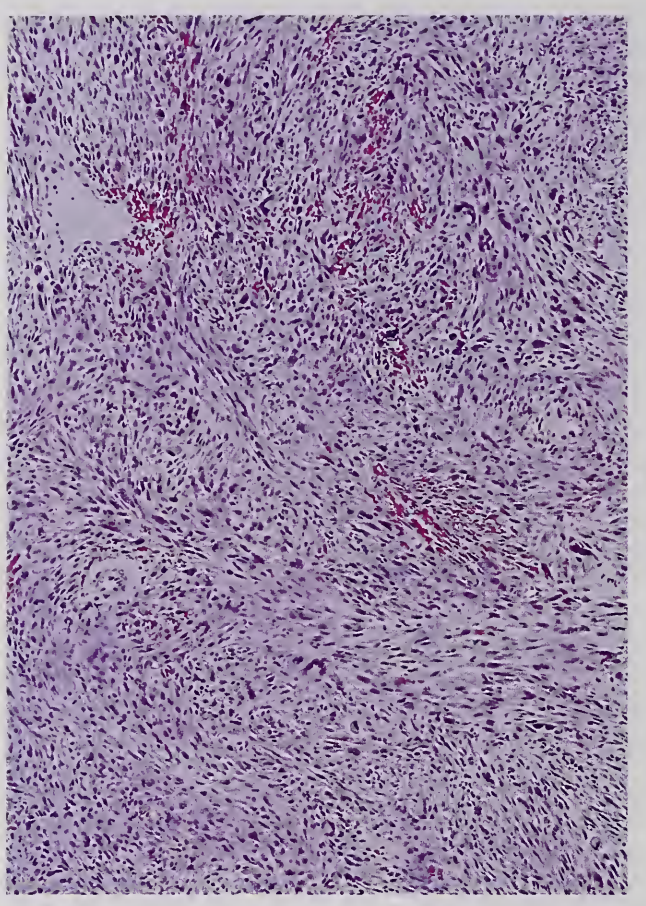


Figure 7-61

MALIGNANT FIBROUS HISTIOCYTOMA

The tumor cells have eosinophilic cytoplasm, are arranged in a swirling interlacing pattern, and have moderate to marked nuclear pleomorphism. Tumor giant cells are present. (Courtesy of Dr. John Reith, Gainesville, FL.)

MFH has an infiltrative growth pattern and marked nuclear pleomorphism with tumor giant cells and multinucleated cells. Cells with large pleomorphic nuclei containing multiple prominent nucleoli and abundant eosinophilic cytoplasm are admixed with smaller round to spindle-shaped cells with moderate nuclear pleomorphism (fig. 7-61). Mitotic figures are usually present and may be numerous and atypical. The spindle cells are arranged in a storiform pattern or in interlacing bundles. The cells of MFH usually contain alpha-1-antitrypsin and alpha-1-antichymotrypsin, either or both of which are identified in approximately 80 percent of cases.

The most commonly described variants of MFH are an *inflammatory type*, which contains many acute inflammatory cells; a *giant cell variant (giant cell tumor of soft parts)*, which contains giant cells with osteoclast-like features but no osteoid or bone; and a *myxoid variant (myxofibrosarcoma)* containing a prominent hypocellular myxoid component (221,449,450). The *angiomatoid variant,* containing prominent blood vessels and blood-filled spaces, is now classified as a separate entity by World Health Organization (WHO).

MFH is locally invasive and large. Involvement of the underlying fascia increases the risk of local or distant metastasis (87,450). The treatment is wide local excision (partial vulvectomy) or radical (total) vulvectomy. Patients with clinical evidence of regional lymph node involvement should undergo regional lymphadenectomy. Postoperative radiotherapy appears to reduce local recurrences. Approximately half of the patients have recurrences or die of metastatic disease.

Fibrosarcoma

Fibrosarcoma is a rare primary tumor of the vulva. A single case has been reported (300). On microscopic examination, the tumor was poorly circumscribed and composed of spindle cells arranged in fascicles with moderate to marked pleomorphism and nuclear atypia with associated collagen. There were 4 mitotic figures per 10 high-power fields. The patient was treated with total deep vulvectomy, however, metastases to the lung and ribs occurred within 6 months, and death from tumor 7 months following surgery.

Angiomyofibrosarcoma (Angiomyofibroblastoma with Sarcomatous Transformation)

Angiomyofibrosarcoma is a high-grade sarcoma resembling MFH. It arose within an angiomyofibroblastoma in an elderly woman (299). Microscopic examination of the sarcomatous area demonstrated marked nuclear atypia and mitoses. The tumor did not express desmin, as seen in typical angiomyofibroblastoma. It did express vimentin, but not CD34, S-100 protein, keratin, or actins.

Synovial Sarcoma

Synovial sarcoma has been reported as a primary vulvar sarcoma (296). Of two reported cases, both occurred in women in their thirties and both presented as painless vulvar masses under 2 cm in diameter. On microscopic examination, epithelial

type cells formed glandular and papillary areas, with associated solid clusters. The cells were surrounded by spindle cells. Immunohistochemical studies demonstrated cytokeratin reactivity in the epithelial type cells and vimentin reactivity in the spindle cells.

Both reported patients were treated with local excision. One patient had a local recurrence; the other was disease free at 4 years follow-up. The differential diagnosis includes epithelioid sarcoma, malignant rhabdoid tumor, benign or malignant epithelial tumor, and endometriosis (298).

Epithelioid Sarcoma

Epithelioid sarcoma involving the vulva is considered to be of proximal type, to distinguish tumors involving the trunk from peripheral tumors that involve the extremities. The tumor has been reported in women of reproductive age and in pregnancy, but is rare in the vulva, where it can arise in the labia majora, subclitoral area, and Bartholin gland area (156,163,198,213, 277,422,428). The tumor is subcutaneous, often multinodular, and usually originates in the reticular dermis, but may arise in deeper soft tissue (422,428).

On gross examination, epithelioid sarcoma has a multinodular appearance. On microscopic examination, the nodules are composed of epithelial-appearing, large rounded cells resembling squamous epithelial cells; areas of necrosis may be seen. The tumor cells have eosinophilic cytoplasm and moderately pleomorphic nuclei, and may resemble rhabdoid cells. Metaplastic bone and cartilage may be present. Epithelioid sarcoma with rhabdoid features has also been observed (156).

Immunohistochemical studies demonstrate immunoreactivity to cytokeratin, EMA, and vimentin. The tumor may also express desmin, CD34, and smooth muscle actin (298). Some cases are immunoreactive for HMB45 as well as CEA (156). The immunoreactivity is similar to that of synovial sarcoma, supporting a common origin (63). The presence of cytokeratin distinguishes these tumors from histiocytic and inflammatory conditions (238,272).

The differential diagnosis includes squamous cell carcinoma, undifferentiated carcinoma, and malignant rhabdoid tumor. Other tumors with epithelioid features included in the differential diagnosis are malignant peripheral nerve sheath tumors with epithelioid features, malignant melanoma, and rhabdomyosarcoma. In contrast to squamous cell carcinoma, epithelioid sarcoma lacks keratinization, intracellular bridges, and an intraepithelial component. Undifferentiated carcinomas typically have distinguishing immunohistochemical features that are not found in epithelioid sarcoma (169,217). The diagnostic features of malignant rhabdoid tumor are summarized below (see Malignant Rhabdoid Tumor). Nerve sheath tumors express S-100 protein and other nerve sheath–related immunohistochemical features. Melanomas usually express Melan-A (see Melanoma). Epithelioid sarcomas also have distinguishing electron microscopic features that are described in literature on soft tissue tumors.

Treatment is wide excision (deep partial vulvectomy) with regional lymphadenectomy and local radiation therapy. The tumor may recur locally and involve regional nodes, but rarely metastasizes to distant sites (202).

Malignant Rhabdoid Tumor

Malignant rhabdoid tumor is a rare soft tissue malignant neoplasm of uncertain origin. It presents as a subcutaneous mass deep to the labium majus that can involve the deep dermis, and as a mass resembling a Bartholin abscess in young women of reproductive age (180,325).

The tumor is typically multinodular and firm, with poorly defined margins. In the vulva the tumor may be under 2 cm in diameter, however, there are insufficient cases at this site to determine the size range.

The tumor may be solid or have an alveolar growth pattern. It contains lobulated aggregates of cells that invade the subcutaneous tissue and dermis, often in a finger-like pattern (fig. 7-62). Areas of hemorrhage within the tumor may give an angiomatoid appearance. The tumor cells are large and polygonal, with eccentric vesicular nuclei and prominent nucleoli. The nuclei are pleomorphic and mitoses are common. The cytoplasm is eosinophilic, resembling that of rhabdomyoblasts or squamous carcinoma cells. Eosinophilic cytoplasmic inclusions are present, some of which indent the nucleus and give the cells a signet ring appearance (fig. 7-62). Electron microscopy demonstrates that these inclusions are composed of intermediate filaments.

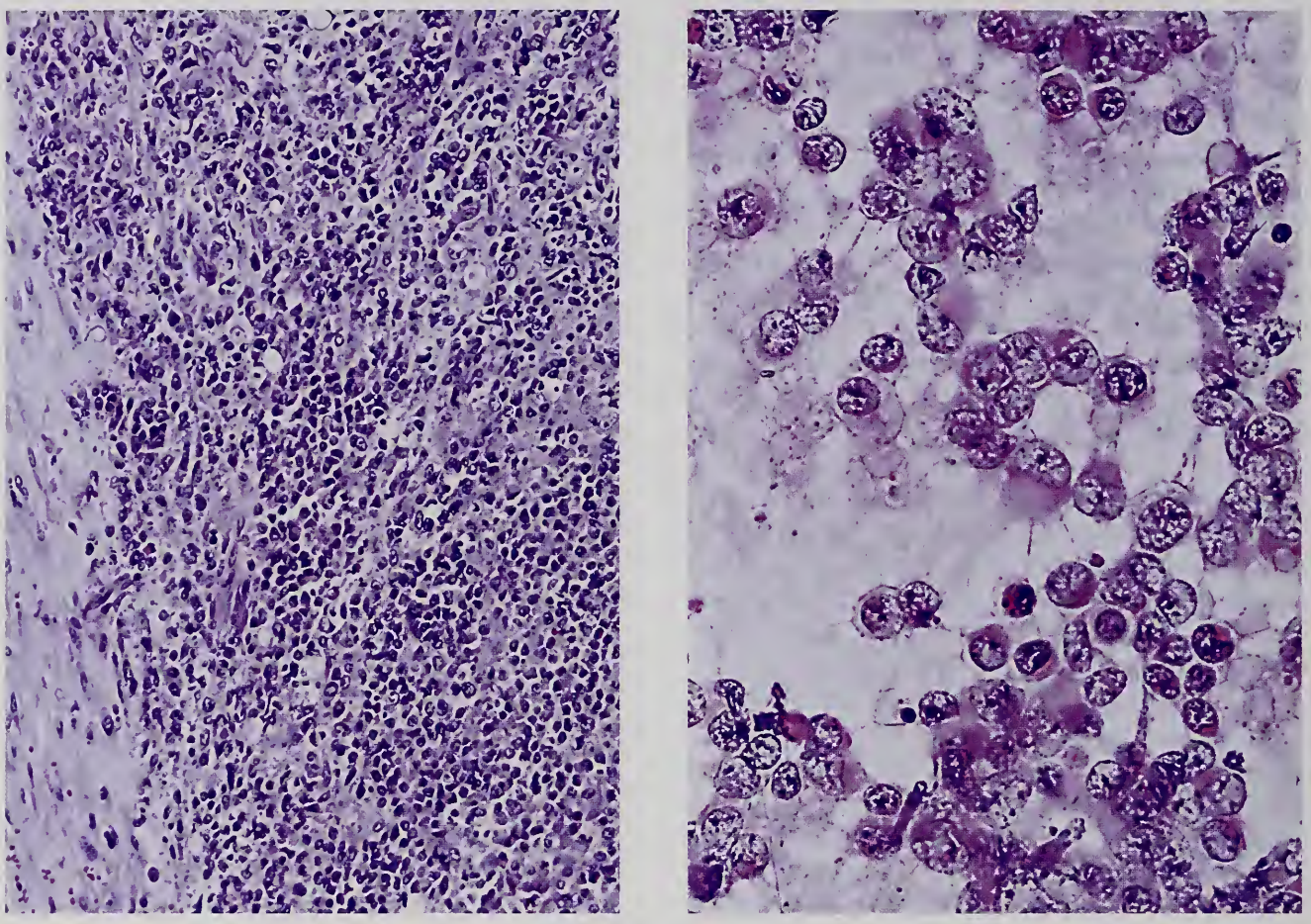


Figure 7-62

MALIGNANT RHABDOID TUMOR

Left: Large and polygonal tumor cells with prominent eosinophilic cytoplasm are in cords and nests. Nuclei are eccentric and vesicular with prominent nucleoli. Eosinophilic cytoplasmic inclusions indent the nuclei in some cells.

Right: In this cytologic imprint, the tumor cells are large and polygonal and have eccentric nuclei with vesicular chromatin and prominent nucleoli. The cytoplasm is eosinophilic and some cells have eosinophilic cytoplasmic inclusions that indent the nucleus.

The immunohistochemical findings are essentially the same as those found in epithelioid sarcoma. Both tumors are immunoreactive for cytokeratin (AE 1/3, MAK 6, CAM 5.2) and EMA. Both may also contain human milk fat globulin-2 and CEA. Actin may be weakly immunoreactive or absent and desmin and S-100 protein antigen are absent (325).

The distinction between epithelioid sarcoma and malignant rhabdoid tumor depends on the light microscopic identification of the lobulated architecture of the rhabdoid tumor, the absence of necrosis, and the granulomatous appearance of epithelioid sarcoma. The typical large tumor cells of malignant rhabdoid tumor, which contain cytoplasmic inclusions and pleomorphic nuclei, are not present in epithelioid sarcoma. The distinction is important because epithelioid sarcomas are indolent and are treated by wide local extended excision, whereas malignant rhabdoid tumors are aggressive and may metastasize. Electron microscopy does not assist in the differential diagnosis unless the character of cytoplasmic inclusions is in question; the presence or absence of intermediate filaments within the inclusions are then determined (325).

Although only a few cases have been reported, extended wide local excision to the fascia or total vulvectomy with bilateral inguinal-femoral lymphadenectomy appears to be the initial surgical procedure of choice (325).

Malignant Schwannoma

Malignant schwannoma has been reported to involve the labia minora, labia majora, and other vulvar sites (225,238,414,417). It occurs almost exclusively in women of reproductive age. Approximately half of the patients also have neurofibromas or von Recklinghausen disease. Clinical presentation is that of a firm subcutaneous mass.

Malignant schwannoma has a homogeneous fibrous-appearing cut surface. A nerve trunk may be attached to the tumor. The tumor is highly cellular, with numerous mitotic figures. Nuclear palisading is usually present. Heterologous elements include cartilage, glandular epithelium, and striated muscle. The tumor is immunoreactive for S-100 protein in half of the cases (452).

Although the prognosis cannot be determined accurately because of the limited number of reported cases, local recurrence and pulmonary metastasis have occurred. Therapy is wide local excision to and including the fascia. Regional lymphadenectomy is of little value and radiotherapy is thought to be ineffective (417).

Lymphangiosarcoma

Lymphangiosarcoma related to congenital nonhereditary lymphedema has been reported in the pubic area of a patient who had lymphedema involving the genital area and leg (60). Lymphangiosarcoma is usually solid in appearance, with poorly defined margins (see Angiosarcoma). Treatment is wide local excision with radiation therapy to the tumor site (60).

Angiosarcoma

Angiosarcomas are rare on the vulva (238,300). Perianal angiosarcomas have been described after pelvic radiotherapy (243). Angiosarcomas are usually solid, deep red tumors with infiltrative margins. The tumor contains variable-sized slit-like vessels that extensively anastomose. The tumor cells forming these vascular spaces have enlarged, pleomorphic, hyperchromatic nuclei with mitotic activity. In poorly differentiated areas, the tumor may appear solid. CD31 is a specific marker; CD34 is less specific but can also be demonstrated in the tumor cells immunohistochemically (151). Von-Willebrand factor (VWF) may be expressed, especially in the epithelioid variant, which may also express cytokeratin (202).

Kaposi Sarcoma

Kaposi sarcoma involving the vulva has been reported (4,238). The early clinical presentation may be a macular lesion, which changes from a macule to a plaque and then to a nodular lesion as the disease progresses. Typically, multiple lesions are present at initial presentation. Kaposi sarcoma is generally considered a primary malignant neoplastic process; however, it may have features more closely resembling a reactive process. Herpesvirus type 8 (HHV-8) is associated with Kaposi sarcoma.

In the macular phase, the tumor is within the dermis and shows increased vascularity and irregular-shaped vascular channels surrounded by mononuclear cells. In the later-observed plaque phase, the vessels are more numerous and associated with atypical spindle cells within the dermis (fig. 7-63). In the advanced nodular phase, one or more violaceous skin nodules are present in a highly vascular spindle cell neoplasm with slit-like anastomosing spaces containing red blood cells.

Many of the neoplastic cells of nodular Kaposi sarcoma are immunoreactive for CD31 and CD34, and generally weakly reactive for *Ulex europaeus* lectin antigen or VWF. The tumor cell nuclei typically express HHV-8 immunoreactivity (18). Desmin may also be expressed (13,18).

Kaposi sarcoma must be distinguished from bacillary (epithelioid) angiomatosis, fibrohistiocytic tumors, benign vascular tumors, vascular scar, and other vascular skin changes that have a clinical presentation and morphologic features similar to Kaposi sarcoma. Bacillary angiomatosis can be diagnosed with a Warthin-Starry stain or immunohistochemical techniques on fresh or formalin-fixed tissue employing bacteria-specific antibodies that demonstrate the bacterial rods of *Bartonella (Rochalimaea) henselae* (73,240,352). The organism can also be cultured. Fibrohistiocytic tumors are usually immunoreactive for alpha-1-antitrypsin, alpha-1-antichymotrypsin, and human mesothelial cell membrane antibody (HBME). A storiform appearance that lacks irregular vascular spaces assists in identifying fibrohistiocytic tumors. Benign vascular tumors are typically well circumscribed, with well-defined vascular spaces. Scars usually have a gross appearance distinctive from that of Kaposi sarcoma, lack skin appendages, and are more fibrous with far fewer vessels.

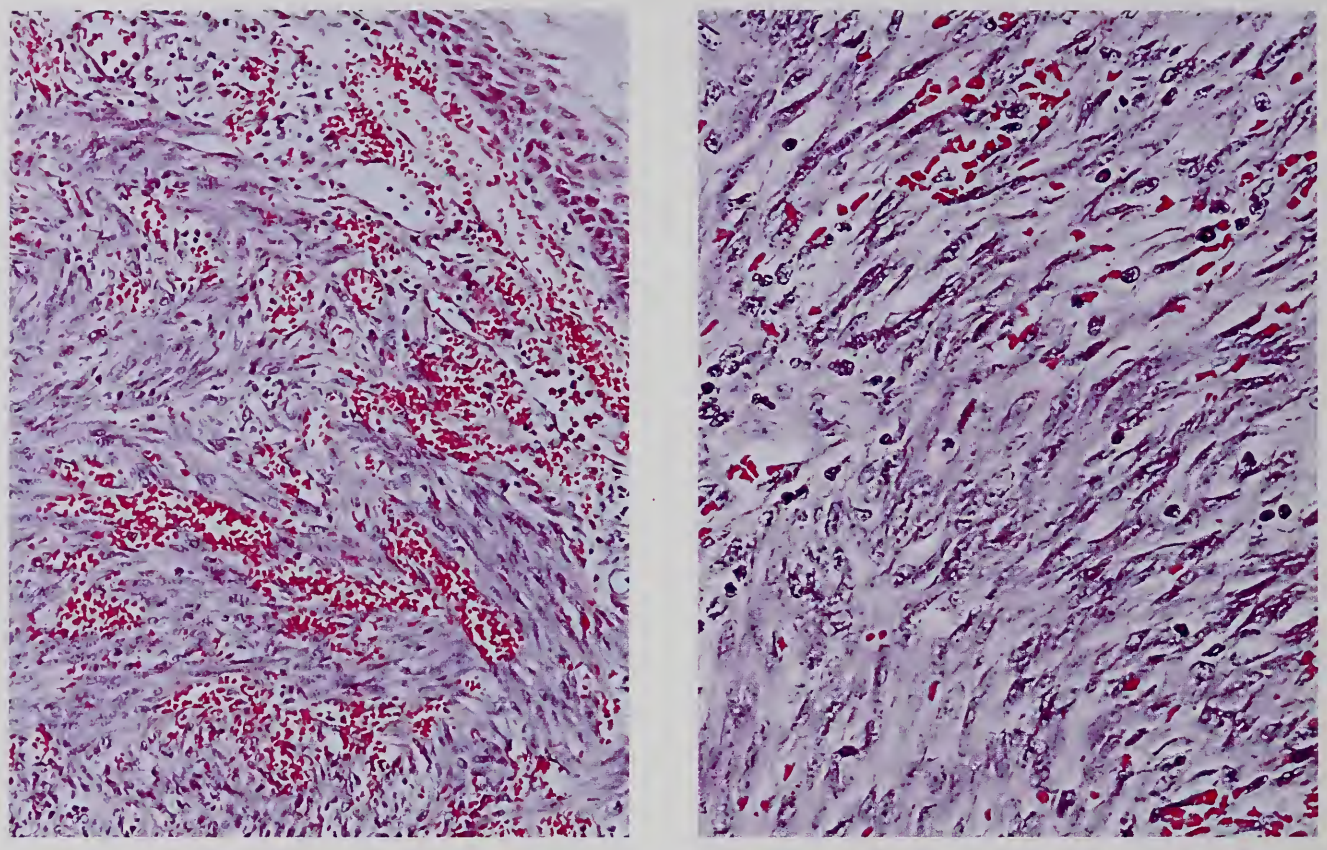


Figure 7-63

KAPOSI SARCOMA

Left: Beneath the epithelial surface, a cellular neoplasm is composed of spindle-shaped cells. Numerous slit-like, blood-filled spaces are surrounded by spindle cells that have minimal nuclear pleomorphism.

Right: The spindle cells have moderate nuclear pleomorphism and prominent eosinophilic cytoplasm. Slit-like blood-filled spaces are present.

Hemangiopericytoma

Hemangiopericytoma is a rare primary tumor of the vulva (87,252,348,486). A congenital hemangiopericytoma of the clitoris has been reported (39).

The tumor is composed of small, uniform, spindle-shaped pericytes associated with a complex capillary component. The vessels have a stellate or staghorn arrangement. Reticulin stains demonstrate that the tumor cells lie external to the vascular spaces and are individually invested by fibrils. Significant cellular atypia is unusual. Hemangiopericytomas may resemble monophasic synovial sarcomas or angiosarcomas.

Immunohistochemical studies are valuable to confirm the diagnosis. The pericytes in half of these cases are immunoreactive for CD34, and one third are immunoreactive for CD57. The tumor cells may also express factor XIIIa. CD31 is not immunoreactive in the tumor but is immunoreactive in the tumor endothelium. The tumor cells do not express actin, cytokeratins, or CD99. S-100 protein antigen may be negative, but also has been reported to be focally immunoreactive, as has factor VIII (202,238).

Benign hemangiopericytomas tend to be small, have a mitotic count of less than 4 per 10 high-power fields, and lack areas of necrosis or hemorrhage (238). A malignant vulvar hemangiopericytoma was reported that metastasized to the femur (355).

Liposarcoma

Liposarcoma is rare on the vulva. It occurs most commonly in middle-aged women (42,131,303). The tumor presents as a soft, subcutaneous mass unattached to the skin. It has a yellow-white appearance grossly, resembling fat. Myxoid

liposarcomas typically have a gelatinous character, are gray to white, and appear well circumscribed.

Liposarcomas of the vulva are usually of well differentiated (*lipoma-like, sclerosing liposarcoma*) (303). Other histologic variants include *pleomorphic liposarcoma*, which has differentiated lipoblasts comprising some of the tumor, and *dedifferentiated liposarcoma*, a liposarcoma associated with an atypical lipomatous tumor (202). Vulvar liposarcoma is usually composed of neoplastic adipocytes, some of which contain atypical nuclei, arranged in poorly defined lobules (131,141). *Myxoid liposarcoma* is infrequent in the vulva. This variant is cellular or paucicellular. Myxoid liposarcomas contain lipoblasts and have a variety of morphologic features, although all have a myxoid stroma and are usually supported by a "chicken wire" vascular framework (238). The tumor cell nuclei are uniform in size and shape. The *round cell liposarcoma* is cellular and the cytoplasm of most of the cells is eosinophilic. Some liposarcomas are immunoreactive for S-100 protein antigen.

Treatment of liposarcoma of the vulva is complete excision (partial deep vulvectomy). Postoperative radiotherapy has been suggested but experience is limited (478). Prognosis is generally good, although the tumor may recur locally. Recurrences can be successfully treated by reexcision (202,303).

Malignant Granular Cell Tumor

Malignant granular cell tumor is distinguished from granular cell tumor by larger size, infiltrative growth, and local recurrence (see Granular Cell Tumor) (361).

MELANOCYTIC TUMORS

Congenital Melanocytic Nevus

Congenital nevi are classified as small if they are under 2 cm in diameter, medium if 2 to 10 cm in diameter, and large if over 10 cm in diameter. Most are small, usually under 0.4 cm in diameter. Large nevi can involve large areas of the body (e.g., garment or bathing suit nevi), and are associated with an increased risk of developing into malignant melanoma with advancing age (254). Small congenital nevi do not carry a similar risk (329).

Common Acquired Melanocytic Nevus

Vulvar nevi are uncommon, occurring in 2.3 percent of women in one series (362). *Acquired nevi* appear in early childhood and continue to develop into early adulthood. Benign nevi are usually under 10 mm in diameter, papular, regular in contour, and uniform in pigmentation. These nevi may be junctional, compound, or intradermal (dermal); the distinction is based upon the location of the melanocytes. The various types are observed with approximately equal frequency within the vulva.

Junctional nevi typically have dendritic nevus cells aggregated within intradermal nests or within the dermal-epidermal junction. They are usually confined to the basal and parabasal areas of the epithelium. Typical dendritic melanocytes are often seen in the adjacent normal epithelium. The *compound nevus* has features of a junctional nevus but also has epithelioid, or less commonly, spindle type nevus cells within the papillary or reticular dermis. The nevus cells may be aggregated or individually surrounded by fibrous tissue within the dermis. An *intradermal nevus*, like a compound nevus, has nevus cells within the dermis; however, the nevus cells are completely confined to the dermis and the junctional component is absent. Within nevi, dendritic and spindle type nevus cells often have melanin pigment, whereas epithelioid nevus cells are usually not pigmented.

Lentigo Simplex

Lentigo simplex is the most common pigmented lesion of the vulva. It is a flat pigmented area on the vulva, usually under 0.5 cm in diameter. It is regarded by some as an early stage in the development of a junctional nevus. Microscopic examination of lentigo simplex reveals a focal increase in melanocytes and melanin pigment in the basal layer. There is usually some hyperplasia of the epidermis, with elongation of the rete ridges, but no melanocytic junctional cell nests. Melanin granules are often found in the epithelium, and pigment-laden melanophages may be seen in the superficial dermis. Lentigo simplex has no clinical significance, although in patients with leopard syndrome, thousands of lentigines are present on the genital and nongenital skin (17).

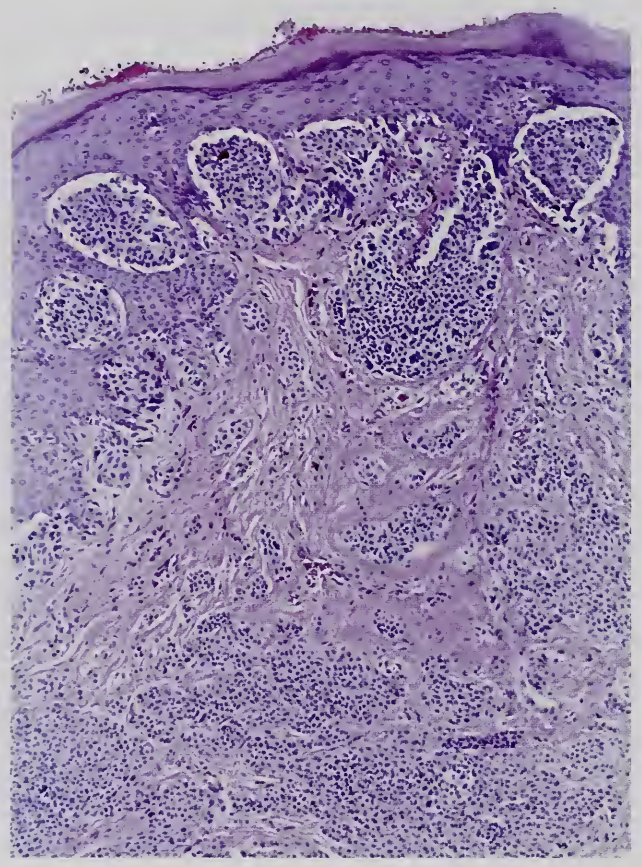


Figure 7-64

ATYPICAL MELANOCYTIC NEVUS

Many junctional nevomelanocytes are seen, some of which are in clusters. There is minimal pagetoid spread. The deeper nevomelanocytic cells are smaller and more mature appearing than those in the junctional area.

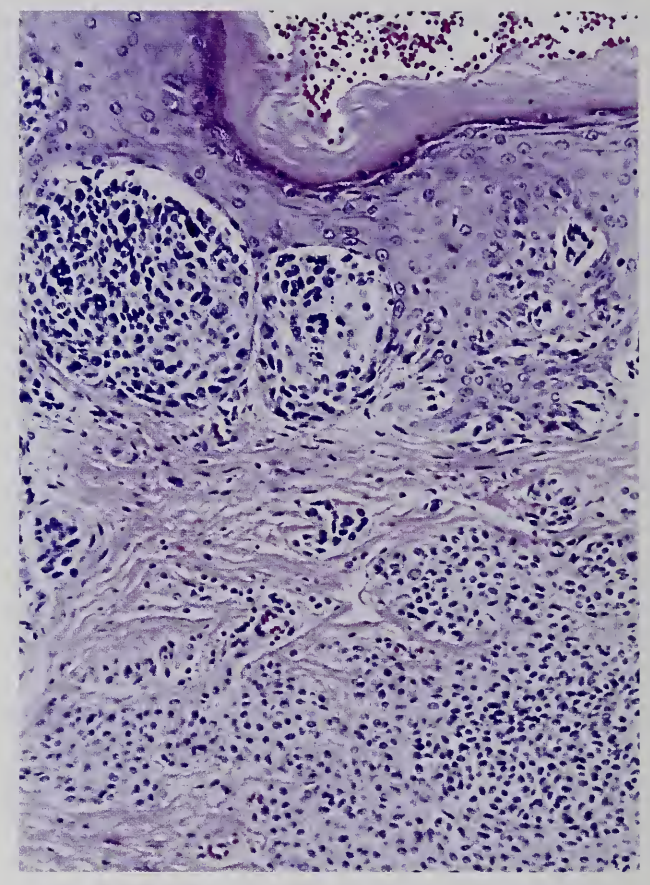


Figure 7-65

ATYPICAL VULVAR NEVUS

Many nevomelanocytes are seen in the junctional, basal, and parabasal areas. The cells in the junctional area are larger and have greater nuclear pleomorphism than the deeper, more mature, nevomelanocytes.

Melanosis Vulvae

Whereas lentigo simplex refers to a small lesion, *melanosis vulvae* describes a larger pigmented area on the vulva, typically 0.5 cm or larger in diameter. Melanosis up to 45 cm in diameter may occur, and may involve the vulva as well as the vagina. It is microscopically indistinguishable from lentigo simplex (362).

Cellular Blue Nevus

Cellular blue nevus is a congenital benign melanocytic nevus that is blue to gray-blue in color. It is rare in the vulva; junctional, compound, and intradermal nevi of the usual type are much more common (162,364). The cellular blue nevus is composed of spindled, dendritic type nevus cells, typically with finely dispersed melanin within the cytoplasm. The nevus cells are aggregated within the dermis by fibrous sclerotic–appearing dermis. They locally infiltrate the adjacent dermis and superficial peripheral nerves (see Malignant Blue Nevus).

Atypical Melanocytic Nevus of Genital Type and Clark/Dysplastic Vulvar Nevus

Atypical vulvar nevi are of two distinct histopathologic types: *atypical melanocytic nevus of genital type* (AMNGT) and *dysplastic nevus (Clark/dysplastic melanocytic nevus)*. Most nevi of the first type are located on the vulva, although the perineum and rarely the mons pubis are involved. The usual appearance is a papular pigmented lesion, usually 5 mm or larger in diameter. The lesion may have somewhat irregular borders and pigmentation.

In a review of 56 cases, the initial diagnosis was melanoma in more than a third, although 36 were AMNGT and 14 were dysplastic nevi (72). These 56 cases occurred in young women, with a reported median age of 25 years.

Atypical Melanocytic Nevus of Genital Type. These nevi are more common on the labium minus and vulvar vestibular mucosa near or on the clitoris (72). AMNGTs have prominent, variable-sized junctional melanocytic nests (figs. 7-64, 7-65). Although some features may suggest a diagnosis of melanoma, the lesion is small, well circumscribed, and lacks pagetoid spread, necrosis, or mitotic activity in the dermis (70,120). In addition, the associated underlying stroma lacks the changes seen with melanoma or Clark/dysplastic nevus, having a nonspecific dermal pattern (72). Women with AMNGT do not have a recognized risk of subsequent malignant melanoma if the lesion is adequately excised.

Clark/Dysplastic Melanocytic Nevus. Dysplastic melanocytic nevi are rare on the vulva. They are usually identified in women of reproductive age. When present, they are more common on the labium majus (72). Clark/dysplastic nevi clinically present as papular lesions that have irregular borders and may have variability of pigmentation. They are typically greater than 5 mm in diameter and may be associated with dysplastic nevi at other sites.

Clark/dysplastic nevi typically have a low-power microscopic appearance of a large junctional nevus. They display architectural disorder as well as cytologic atypia; however, there can be a considerable spectrum in the degree of architectural disorder and atypia, and some cases may show predominately one or the other feature. The Duke grading system has been developed to define these variables and is summarized in Table 7-6 (389a).

The nevus cells may be clustered in intraepithelial nests and in skin appendages, including hair shafts and the ducts of sweat glands. A dermal component has spindle or epithelioid type nevus cells in nests or isolated within the papillary and reticular dermis (120,357). The nevus cells are large and epithelioid or spindle shaped, with variable nuclear pleomorphism and may have prominent nucleoli. The underlying stromal response can resemble that of melanoma, with concentric eosinophilic fibroplasia and lamellar fibroplasia (72).

Table 7-6

DUKE GRADING SYSTEM FOR CLARK NEVI (DYSPLASTIC NEVI)[a]

Architectural Disorder[b]	0	1
Junctional component nested at both edges	Yes	No
Good overall symmetry	Yes	No
More than 5 percent of nests cohesive	Yes	No
Suprabasal spread prominent, or present at edge	No	Yes
Confluence of >50 percent of proliferation	No	Yes
Single cell proliferation absent or focal	Yes	No
Cytologic Atypia[c]	0	1
Nuclei round or oval, and euchromatic	Yes	No
Nuclei > basal layer keratinocyte nuclei	No	Yes
Nucleoli prominent	No	Yes
Cell diameter >2X basal layer keratinocyte nuclei	No	Yes

[a]Adapted from data in reference 389a. A separate score is obtained for architecture and cytology by assigning a value of 0 or 1 for each criterion and summing.
[b]0-1 = mild; 2-3 = moderate; 4-6 = severe.
[c]0-1 = mild; 2 = moderate; 3-4 = severe.

Microscopic Features that Distinguish Clark/Dysplastic Nevus and AMNGT from Melanoma. Growth, as seen on full cross section of the nevus, is symmetric. A line perpendicular to the surface drawn through the center of the nevus demonstrates that each half is a mirror image of the other. The most atypical cells are in the superficial levels of the nevus, with more mature, smaller, and more uniform cells present in the deeper dermis. Although pagetoid spread of single melanocytes may be present, there is minimal or no involvement of the superficial one third of the epithelium (3,40,357).

Clinical Findings that Distinguish Clark/Dysplastic Nevi from AMNGT. Clark/dysplastic nevi are more commonly on the labium majus and may be associated with *dysplastic nevus syndrome*. Dysplastic nevus syndrome includes multiple large nevi, usually over 0.5 cm in diameter, that involve the trunk, extremities, and vulva. AMNGTs are more common on the labium minus and mucosa on or about the clitoris, and are not associated with nevi of similar type in nongenital locations, although more than one AMNGT may be present on the vulva.

Microscopic Features that Distinguish Clark/Dysplastic Nevi from AMNGT. These

changes are primarily related to the dermis about the nevus cells. Clark/dysplastic nevi have dermal findings similar to melanoma, with concentric eosinophilic fibroplasia and lamellar fibroplasia. AMNGTs lack the dermal features of melanoma (72).

Prognostic Features that Distinguish Clark/Dysplastic Nevi from AMNGT. Clark/dysplastic nevi are associated with dysplastic nevus syndrome, which carries a risk of subsequent malignant melanoma. AMNGT has no recognized significant melanoma risk after complete excision.

Malignant melanoma is included in the differential diagnosis of both of these types of nevi.

Malignant Melanoma

General Features. *Vulvar melanoma* accounts for approximately 3 percent of all melanomas in women. Approximately 9 percent of all malignant tumors of the vulva are melanomas. These tumors are observed predominantly in white women and the frequency increases with advancing age (448); the mean age at diagnosis is 55 years of age (316). Malignant melanoma of the vulva, however, associated with lichen sclerosus was observed in a 10- and 14-year-old (121,172). In a study of 198 women, the age-specific incidence of malignant melanoma was 1.28/100,000 for women 75 years of age and older, 0.56/100,000 for women 45 to 59 years of age, and 0.19/100,00 for women 30 to 44 years of age (342). One third of women with malignant melanoma of the vulva are under 50 years of age.

Vulvar bleeding was the most common presenting symptom in one study, and was present in one third of the patients (342). Additional presenting complaints included a mass, ulcer, or pigmented lesion. Pruritus, burning, and dysuria were also experienced. In some cases, the melanoma arose from a preexisting benign or atypical pigmented lesion (71,279,357). In a study of 182 cases, the melanoma arose in glabrous skin in 90 cases, in hairy glabrous skin in 69 cases, and in hair-bearing skin in 23 cases (342).

Melanomas occur on the clitoris, labia minora, and labia majora with approximately equal frequency (331). They are typically slightly elevated or nodular, and usually pigmented (about 75 percent of cases) (fig. 7-66). Pigmented epithelium is adjacent to the melanoma and satellite nodules may be present. Clinically, malignant melanoma may resemble melanosis vulva, nevi, and pigmented VIN. If nonpigmented, melanoma may resemble squamous cell carcinoma or a superficial soft tissue tumor.

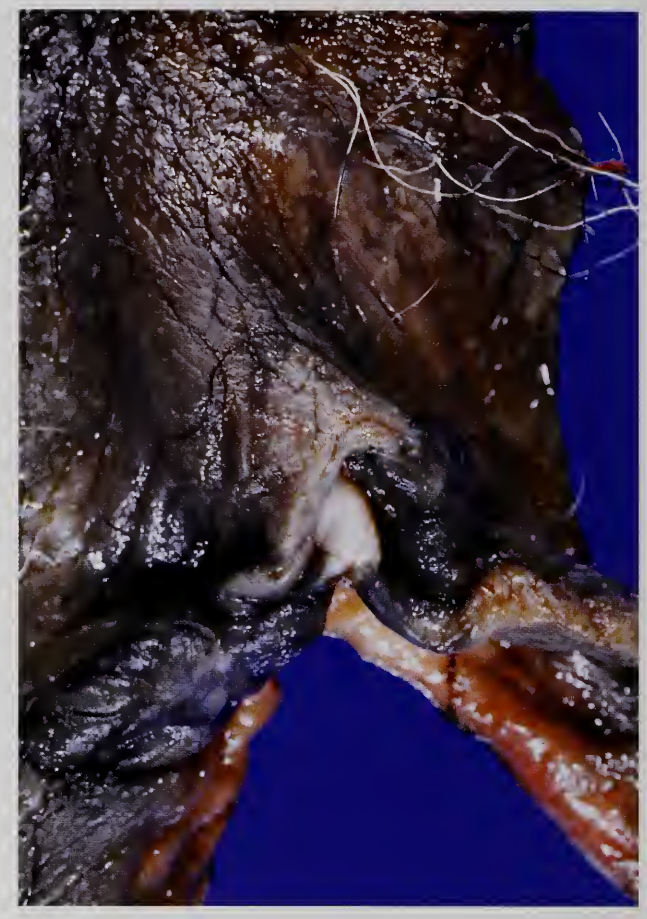


Figure 7-66

VULVAR MALIGNANT MELANOMA, SUPERFICIAL SPREADING

The pigmented tumor from a total vulvectomy involves the right labium minus and has a geographic appearance. This patient also has melanosis vulvae. (Courtesy of Robin Foss, PA, Gainesville, FL.)

Microscopic Findings. Vulvar melanomas are of three histopathologic types: *superficial spreading melanoma, nodular melanoma,* and *mucosal/acral lentiginous melanoma* (24,273,332). The relative frequency of these types differs in various reports. In one study, mixed and unclassifiable cases comprised 25 percent of tumors; 52 percent were of the mucosal/acral lentiginous type (342). In another study, mucosal/acral lentiginous melanoma was the most common type identified (24). Nodular melanoma accounted for

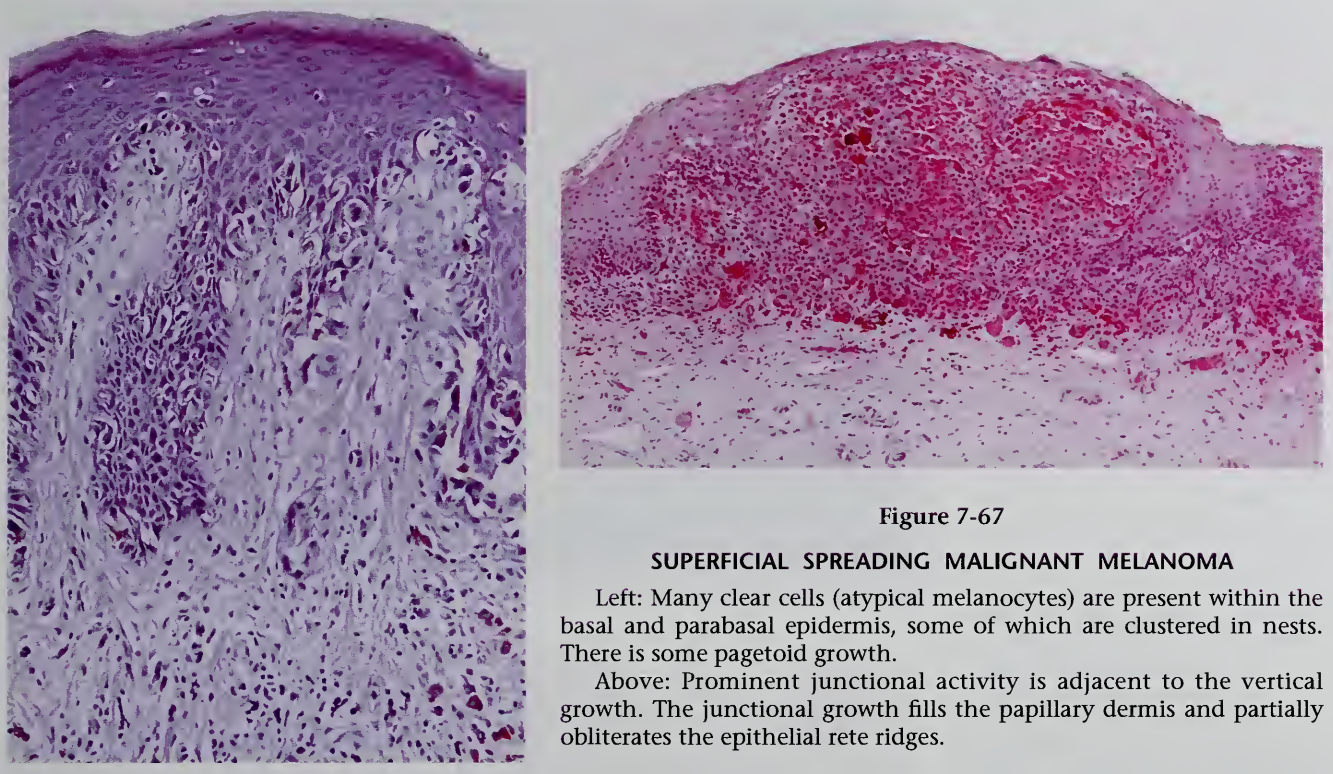


Figure 7-67

SUPERFICIAL SPREADING MALIGNANT MELANOMA

Left: Many clear cells (atypical melanocytes) are present within the basal and parabasal epidermis, some of which are clustered in nests. There is some pagetoid growth.

Above: Prominent junctional activity is adjacent to the vertical growth. The junctional growth fills the papillary dermis and partially obliterates the epithelial rete ridges.

approximately 20 percent of the cases in two series (24,342). Superficial spreading melanoma is generally the least common type of melanoma encountered in the vulva, accounting for 4 percent of 198 cases in one series (fig. 7-67) (342). The vulvar melanoma type related to fatal outcome in one study of 14 patients who died of vulvar melanoma, 65 percent had nodular melanoma: 21 percent had superficial spreading melanoma, and 14 percent had mucosal/acral lentiginous melanoma (189).

Some variation in reported frequency of these melanoma types may relate to differences in the criteria used to distinguish superficial spreading melanoma from nodular melanoma. Superficial spreading melanoma can be differentiated from nodular melanoma by evaluating the adjacent epithelium. If the radial growth of a melanoma, or atypical melanocytes, involves four or more adjacent rete ridges, the tumor should be classified as superficial spreading melanoma (329). Mucosal/acral lentiginous melanomas have both vertical growth, as is seen in nodular melanoma, and radial growth, as is seen in superficial spreading melanoma. Atypical melanocytes are usually identified within the epithelium adjacent to acral lentiginous and superficial spreading melanomas.

Malignant melanomas usually have one of three cellular types: epithelioid, dendritic (nevoid), or spindle cell. The tumor may be composed of a single type or several types. The cells usually contain melanin in variable amounts, ranging from minimal to large quantities; however, amelanotic tumors do occur.

The histopathologic features can be correlated with the melanoma subtype. The invasive malignant melanocytic cells of a superficial spreading melanoma typically are large, with relatively uniform nuclei and prominent nucleoli. The intraepithelial malignant melanocytic cells within the radial growth portion of the tumor have similar cellular features. These neoplastic melanocytes are usually within the epithelium, distributed in the junctional areas as well as in a pagetoid manner throughout the epithelium.

Nodular melanomas predominantly have an invasive component and the intraepithelial adjacent radial growth phase may be minimal (fig. 7-68). They have cells that are polygonal (epithelioid) or spindle shaped. Polygonal cells typically have large nuclei, with prominent nucleoli and eosinophilic cytoplasm. Dendritic cells have moderate nuclear pleomorphism and tapering cytoplasmic extensions. The spindle cells have small, oval nuclei.

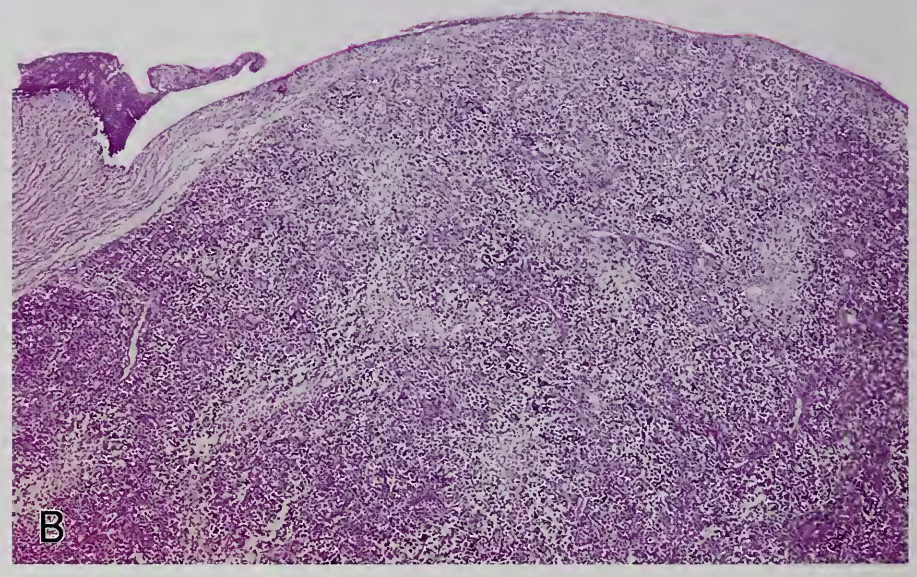
Figure 7-68

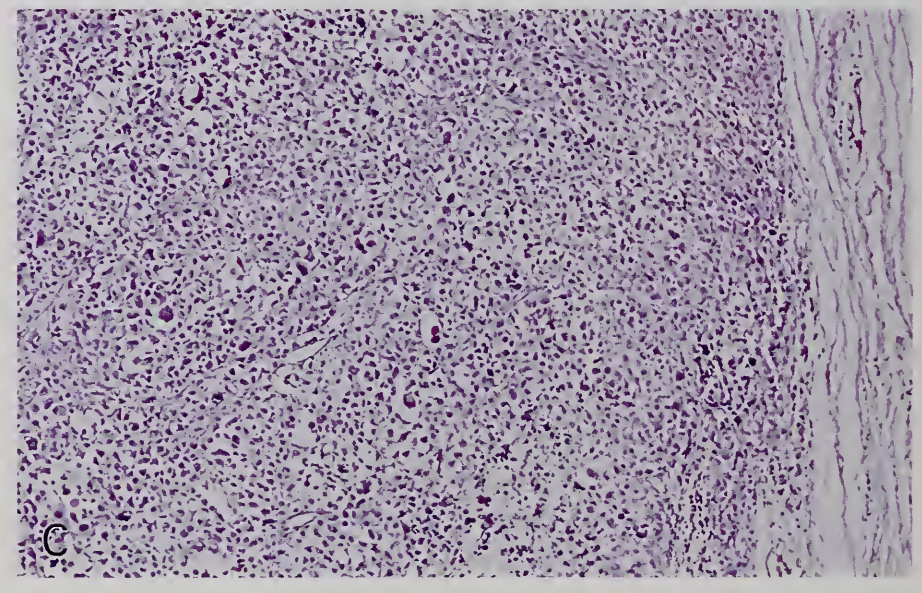
MALIGNANT MELANOMA, NODULAR

A: The melanoma is nodular and pigmented. It involves the inferior labia majora and extends into the vagina. (Courtesy of Robin Foss, PA, Gainesville, FL.)

B: Cross section of the melanoma at its junction with the surface epithelium. The adjacent epithelium is not involved by tumor. The melanoma protrudes from the surface and is within the dermis.

C: The nodular tumor, in its deep location, is highly cellular and moderately pleomorphic. There is little melanin.





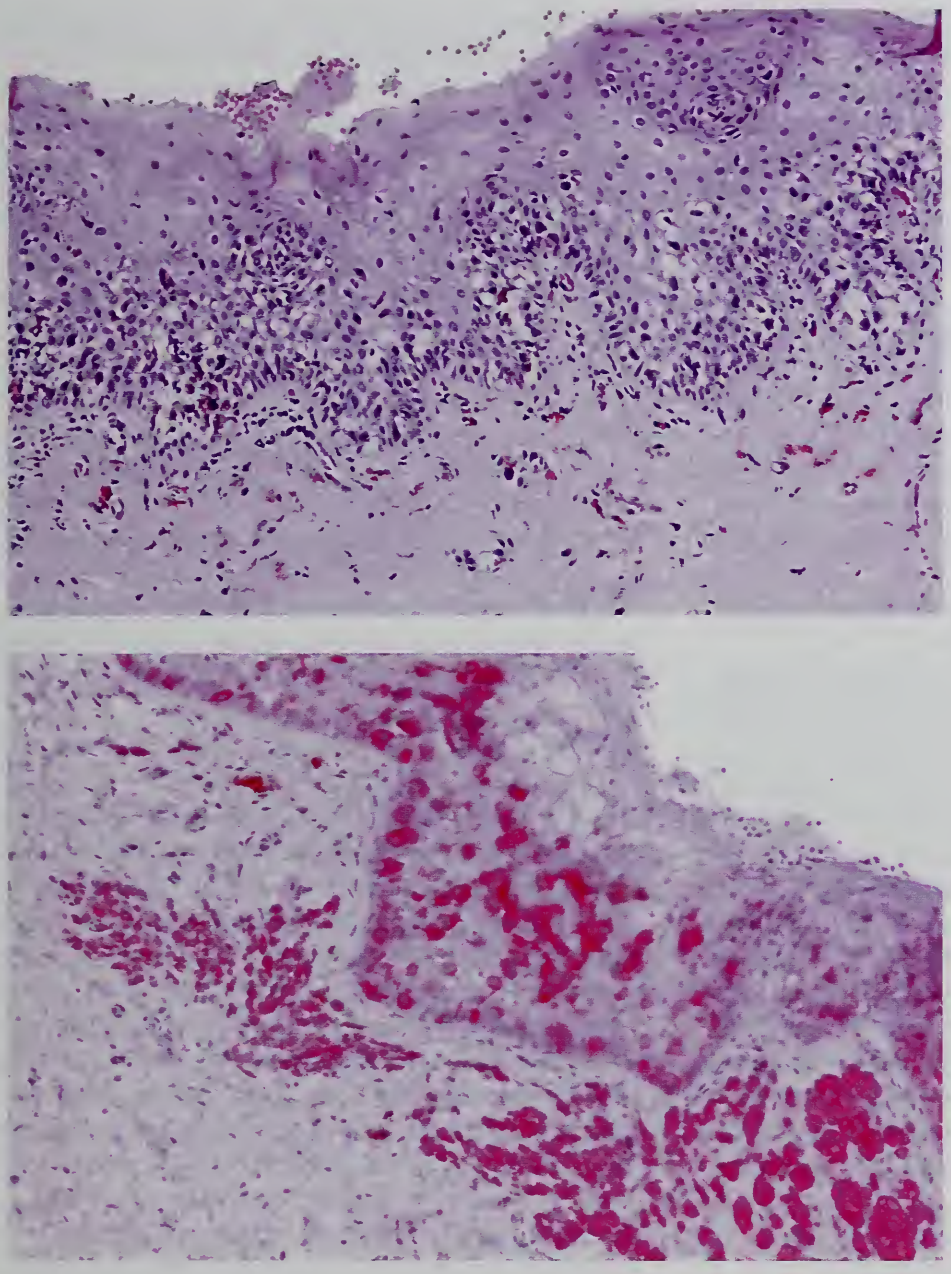


Figure 7-69

MUCOSAL ACRAL LENTIGINOUS MELANOMA

Top: The tumor is composed of spindle- to oval-shaped melanocytes, some of which have prominent clear cytoplasm. The melanoma cells are predominantly within the basal epithelial layer; some are within the superficial dermis (see right figure). There is a minimal pagetoid spread.

Bottom: Immunohistochemical study with Melan-A and red chromagen shows immunoreactive melanoma cells within the epithelium as well as the superficial dermis. The pagetoid spread is more evident after staining.

Mucosal/acral lentiginous melanomas have minimal or no pagetoid spread. These melanomas usually have junctional spindle cells that are uniform, with little nuclear pleomorphism, and that diffusely invade the adjacent dermis (fig. 7-69). The invasive tumor cells usually are associated with a desmoplastic dermal response.

The prognostic features that are important in the assessment of malignant melanoma include the level of invasion (Clark level) and the thickness of the melanoma (349,412). The five levels of invasion defined in the Clark classification of cutaneous melanomas are applicable to malignant melanomas of the vulva arising in keratinized skin, but may require some modification when assessing melanomas arising within mucocutaneous areas, such as the vulvar vestibule (71). Level I melanoma is melanoma in situ; level II melanoma extends into the superficial papillary dermis; level III melanoma fills and expands the papillary dermis; level IV melanoma invades the reticular dermis; and level V melanoma invades beyond the reticular dermis, involving fat or deeper tissues. Measurements of thickness for cutaneous malignant melanoma, as proposed by

Breslow (36), include measurement from the deep border of the granular layer of the overlying epithelium to the deepest point of dermal invasion by tumor.

These measurement methods have been modified to address mucosal melanomas. The thickness and level of invasion of a vulvar melanoma have been correlated in tumors that involve mucosal, noncutaneous sites in the vulva (71). Level I melanomas have no measurable thickness; level II melanomas have a thickness of 1 mm or less; level III melanomas have a thickness exceeding 1 mm up to 2 mm; and level IV melanomas have a thickness exceeding 2 mm but not involving subcutaneous fat or adjacent deeper structures (71). The presence of lymph node metastasis and the number of lymph nodes with metastatic tumor significantly influence survival (331).

Differential Diagnosis. Malignant melanoma may resemble Paget disease, VIN, and dysplastic nevi (357). The resemblance to Paget disease is greatest in superficial spreading melanomas. The cells of Paget disease are usually larger, have more cytoplasm, and are clustered, with occasional intraepithelial gland-like formation. These cells usually contain mucin. Paget cells of cutaneous or anorectal origin are immunoreactive for CEA and CK7 or CK20, respectively; Paget cells of urothelial origin are immunoreactive for uroplakin III and CK7 or CK20. Melanomas are not immunoreactive for these markers (43,284,461), but are immunoreactive for S-100 protein, Melan-A, HMB45, microphthalmia-transcription factor, and tyrosinase; nonmelanocytic tumors are negative (140,158). Melanin stains are not of value because Paget cells may contain melanin pigment, and amelanotic melanomas may not contain detectable melanin. Melanomas do not contain cytokeratin 54-kD, which is identified in Paget cells.

Squamous cell carcinomas with tumor giant cells or those predominantly composed of spindle cells may resemble malignant melanoma. More typical squamous cell carcinoma may be identifiable adjacent to the giant cell or spindle cell component. Immunohistochemical studies are of value in the differential diagnosis (462).

Spindle cell tumors of soft tissue origin, large cell lymphomas, and metastatic tumors including choriocarcinoma, are included in the differential diagnosis. In these cases, a review of the clinical history and physical and radiologic findings, thorough sectioning of the submitted tissue, and immunohistochemical studies usually provide sufficient evidence to permit an accurate diagnosis. A spectrum of antibodies is used, including epithelial markers (e.g., AE1/3, CK7 and CK20, GCDFP-15, EMA), hematopoietic markers, including those for Ki-1 lymphomas (e.g., leukocyte common antigen [LCA]), muscle markers (e.g., desmin, actin), fibrohistiocytic markers (e.g., alpha-1-antitrypsin, alpha-1-antichymotrypsin), neuroendocrine tumor markers (e.g., S-100 protein, chromogranin, synaptophysin), common adenocarcinoma markers (e.g., CEA), and melanoma markers (e.g., Melan-A, HMB45, S-100 protein). When faced with a poorly differentiated vulvar tumor that defies classification on initial microscopic examination, melanoma should be placed first on the list in the differential diagnosis.

Treatment. Treatment for vulvar melanomas with a thickness of 0.75 mm or less is wide local excision (partial deep vulvectomy) with a 2-cm circumferential and deep margin. Melanomas of greater thickness are treated by wide and deep excision to the fascia (partial deep vulvectomy) (316,425). Depending on the size and location of the tumor, the surgical procedure may include bilateral inguinal lymphadenectomy (474). Radical vulvectomy does not appear to improve survival when compared to wide local excision with bilateral groin lymphadenectomy (316,342,401).

Prognosis. The factors that adversely influence survival include a tumor thickness exceeding 2 mm, Clark level V, increased depth of tumor invasion, a mitotic count exceeding $10/mm^2$, surface ulceration, and a minimal or absent inflammatory reaction (189,474). The depth of tumor invasion is an important prognostic factor. In one study, 16 patients with stage I tumors, tumors with invasion of 1.75 mm or less, did not have recurrence, but all of the patients with deeper tumors did (241). Vascular space invasion and tumor necrosis are also associated with a poorer prognosis and are more commonly seen with large melanomas (329). No recurrences of vulvar melanoma have been observed when the thickness was 0.75 mm or less (328,474). Melanomas at Clark level II or

less, and those with a thickness of 1.49 mm or less are associated with an excellent prognosis. A tumor volume less than 100 mm^3 correlates with an excellent prognosis (22,425).

Following surgical excision, melanomas may recur locally or metastasize to the cervix, urethra, vagina, rectum, and other sites (332). Distant metastasis may be the first sign of recurrence. Metastases to the lung, brain, urinary bladder, bone marrow, and abdominal wall have all been observed (189). Prognosis after recurrence is guarded, with a 5-year survival of approximately 5 percent (332).

Malignant Blue Nevus

Malignant blue nevus has been reported arising in the labium majus of a 28-year-old woman who 15 years later had an ovarian metastasis (403). As in other sites, this tumor may have a low mitotic rate, but significant nuclear atypia.

MISCELLANEOUS TUMORS

Malignant Lymphoma

Primary *malignant lymphoma* of the vulva is rare, although the vulva is second only to the cervix as a primary site of lymphoma in the female genital tract (165). Vulvar malignant lymphoma occurs predominantly in women of reproductive or postmenopausal age. The tumor presents as a mass, sometimes involving the Bartholin gland area (426,439). The overlying epithelium may be erythematous or ulcerated.

The lymphoma is usually of the *diffuse B-cell large cell type*; however, *peripheral T-cell lymphoma, diffuse mixed cell lymphoma*, and *follicular large cell lymphoma* have been reported (439). Some large cell lymphomas, such as *Ki-1 lymphoma*, may resemble carcinomas. The lymphoma usually has a deep pushing border and seldom infiltrates the overlying epithelium (165). The dermal border may be associated with a desmoplastic stromal response, with small isolated groups of neoplastic cells surrounded by fibrous tissue within the deeper adjacent dermis. The cells are monomorphic, unlike those of an inflammatory infiltrate; phagocytosis is typically absent (480).

Immunohistochemical studies, including CD45 (LCA) and other specific markers for T and B cells, flow cytometry, and molecular studies for gene rearrangements, are of great value for identifying and characterizing the lesion as a lymphoma. The differential diagnosis includes lymphoepithelioma-like carcinoma, which expresses cytokeratins in the malignant epithelial cell element, and inflammatory or infectious processes (480). The treatment is chemotherapy; prognosis is dependent on the type and stage of the lymphoma.

TUMORS OF GERM CELL TYPE

Yolk Sac Tumor (Endodermal Sinus Tumor)

Yolk sac tumor (also termed *endodermal sinus tumor*) is a rare primary tumor in the vulva. It is reported to arise in the clitoris or in the labia (58,99,216,430). The patients range in age from 22 months to 26 years.

Microscopic examination characteristically reveals a reticular pattern with irregular spaces lined by primitive epithelial cells; some of the spaces contain single papilla with a central vessel (Schiller-Duval bodies). PAS-positive globules are common. Alpha-fetoprotein is a marker of the tumor; it is detected in the tumor cells by immunohistochemical staining and is elevated in the serum.

The prognosis historically has been guarded. With improved chemotherapy, however, survival has improved for patients with germ cell tumors in general. The current therapy is wide local excision with combination chemotherapy of the type used to treat analogous tumors in the ovary and vagina.

NEUROENDOCRINE AND NEUROECTODERMAL TUMORS

Merkel Cell Tumor

Merkel cell tumors are rare in the vulva, usually presenting as an intradermal nodule or nodules in older women (33,64,77,138). The overlying surface may be erythematous. There are three subtypes of Merkel cell tumors: trabecular (carcinoid-like), intermediate, and small cell (oat cell-like) types. There are insufficient vulvar cases to determine the frequency of these subtypes in the vulva. Glandular and squamous differentiation may be observed. Merkel cell tumor may be associated with VIN or invasive squamous cell carcinoma (33,411).

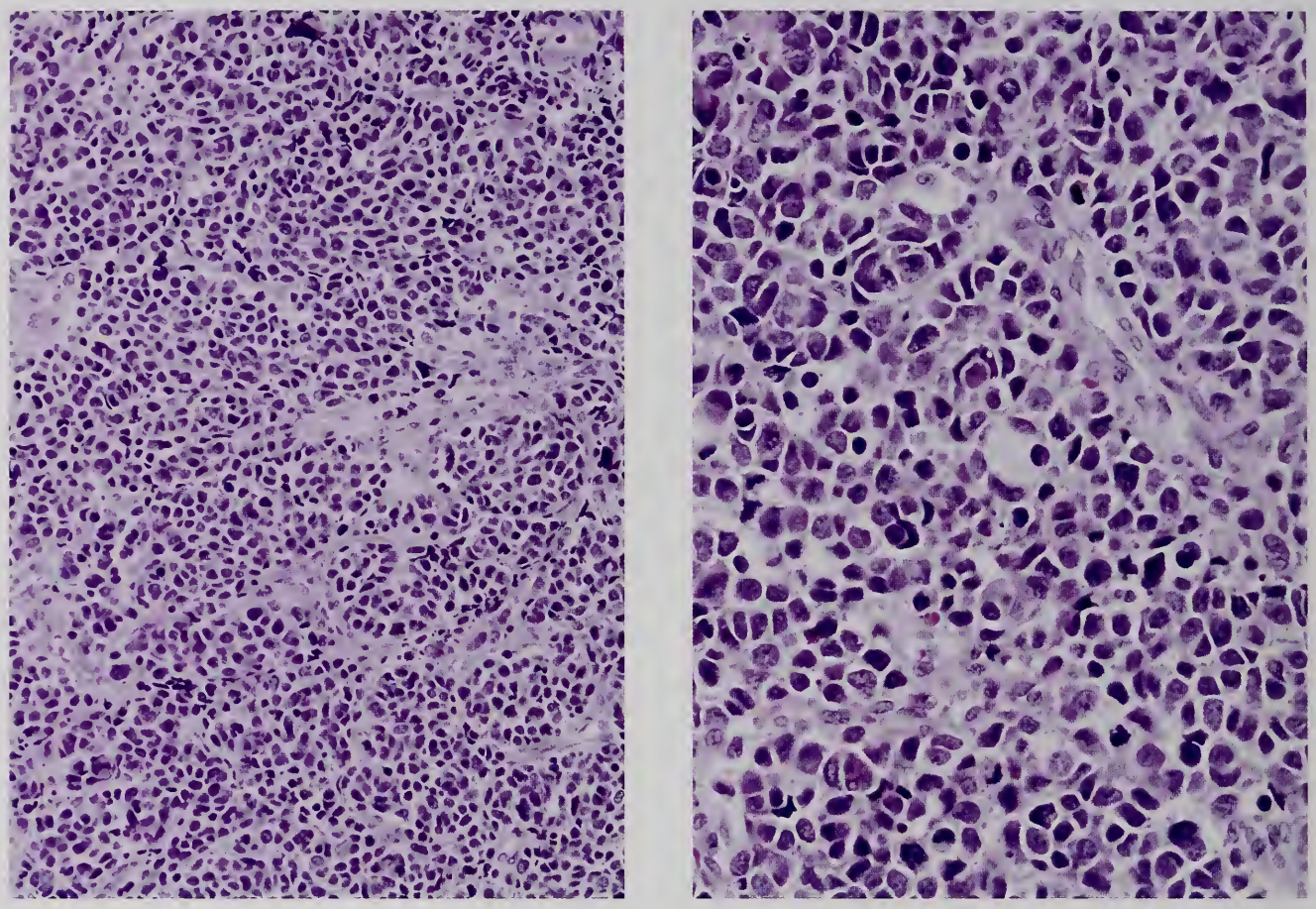


Figure 7-70

MERKEL CELL TUMOR

Left: The tumor within the dermis is composed of uniform small cells with hyperchromatic nuclei in a characteristic punctate chromatin pattern, and little cytoplasm. The mitotic count is high

Right: The tumor cells are small and uniform. The nuclear chromatin is hyperchromatic without prominent nucleoli. Some nuclear moulding and mitotic figures are evident.

Merkel cell tumor lies within the dermis. It is composed of uniform small cells containing hyperchromatic nuclei with a characteristic punctate chromatin pattern, high mitotic activity, and little cytoplasm (fig. 7-70). The tumor is infiltrative and vascular space invasion is common.

The tumor cells are usually immunoreactive for neuron-specific enolase, and may be reactive for the neuroendocrine markers synaptophysin and chromogranin (64,284,440). Tumor cells are also focally immunoreactive for low molecular weight keratin, producing a distinctive perinuclear cytoplasmic dot. Electron microscopy reveals dense core and membrane-bound neurosecretory granules, which were associated with adrenocorticotropic hormone (ACTH) production in one case (179). These findings distinguish this tumor from peripheral neuroectodermal tumor, lymphoma, basal cell carcinoma, and poorly differentiated squamous cell carcinoma, but do not exclude a metastatic tumor with neuroendocrine features. Peripheral neuroectodermal tumor is immunoreactive for CD99. Lymphoma is CD45 immunoreactive; both CD99 and CD45 are negative in Merkel cell tumor. Metastatic small cell carcinoma is usually associated with an evident, current, or past primary tumor in another site.

Merkel cell tumors commonly metastasize to regional lymph nodes with subsequent distant metastasis, often occurring within a year of diagnosis (64,138). The treatment is usually wide local excision (partial deep vulvectomy) with sentinel lymph node sampling. If the sentinel lymph node contains tumor, regional

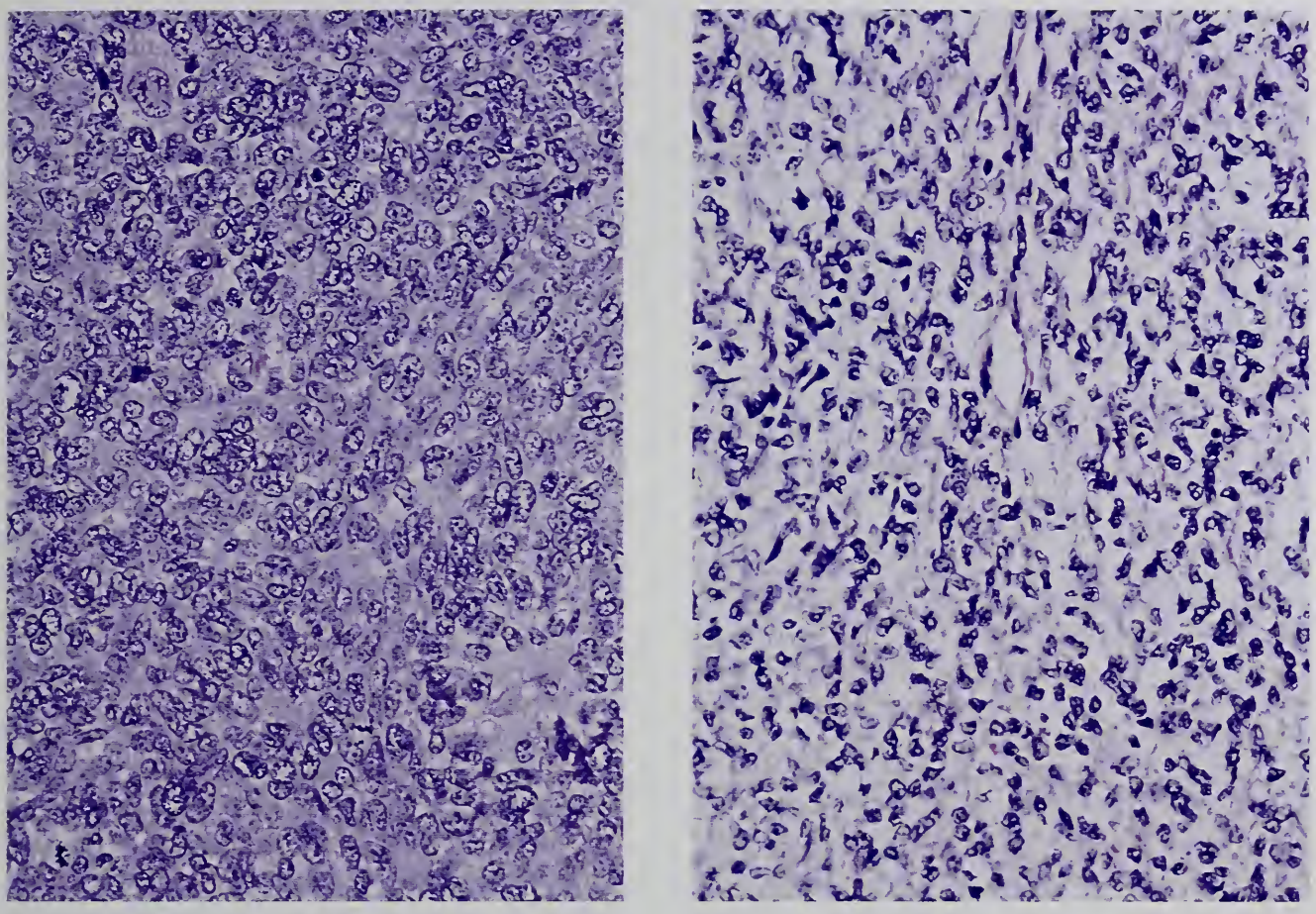


Figure 7-71

PERIPHERAL NEUROECTODERMAL TUMOR

Left: The tumor is composed of small uniform cells with little cytoplasm and poorly defined cell borders. The nuclei are hyperchromatic with finely granular chromatin and rare small nucleoli. The mitotic count is high. The cells are arranged in a multilobulated pattern. Undifferentiated areas, rosettes, pseudorosettes, and sinusoidal-like areas with small cystic spaces are present.

Right: The small uniform tumor cells have nuclei with hyperchromatic and finely granular chromatin, with some small nucleoli. There is scanty cytoplasm and the cell borders are not well defined.

lymphadenectomy and radiation to the primary tumor and regional spread site are recommended. Chemotherapy is used for systemic spread of tumor (64,138,398).

Peripheral Neuroectodermal Tumor (Extraosseous Ewing Sarcoma)

Peripheral neuroectodermal tumor (PNET) (also known as *extraosseous Ewing sarcoma*) is a rare primary tumor of the vulva that has been reported in a child as well as in women of reproductive age (409,440). The tumor presents as a subcutaneous or polypoid mass in the labium majus or minus. The mass may be fluctuant, resembling a cyst, and may be ulcerated.

Microscopically, the tumor is circumscribed but nonencapsulated and composed of small uniform cells with little cytoplasm and poorly defined cell borders (fig. 7-71). The nuclei are hyperchromatic with finely granular chromatin and rare small nucleoli. The mitotic count may be high, exceeding 10 per 10 high-power fields, however, rates as low as 3 per 10 high-power fields have been reported (300,440). The cells are arranged in a multilobulated pattern, but many patterns are seen: undifferentiated areas, rosettes, sinusoidal-like areas with small cystic spaces with eosinophilic proteinaceous material, follicle-like structures, and Homer-Wright rosettes (409,440).

The cytoplasm stains with PAS and digests with diastase. Strong cytoplasmic immunoreactivity for CD99 and vimentin is typically present. Focal reactivity for synaptophysin may be observed. Pancytokeratin does not delineate a perinuclear cytoplasmic reactive area, as seen in Merkel cell tumor, but is focally immunoreactive in some cases. Other neuroendocine markers are reportedly negative (440). Neuron-specific enolase was immunoreactive in one case (409).

Electron microscopy does not demonstrate dense core neurosecretory granules, but shows mesenchymal cells with rudimentary cell junctions, cytoplasmic mitochondria, and smooth and rough endoplasmic reticulum. Approximately 90 percent of tumors have the chromosomal translocation t(11;22)(q24;q12). Chromosome analysis, fluorescence in situ hybridization, or reverse transcriptase-polymerase chain reaction (RT-PCR) can detect evidence of this translocation (440).

Treatment is usually local wide and deep excision (partial deep vulvectomy). Radiation therapy to the tumor field is combined with surgery. Chemotherapy has also been used in these tumors. There is insufficient evidence currently to determine overall prognosis (440). One patient was treated with partial total deep vulvectomy with radiation and chemotherapy but died 10 months later with pulmonary metastases (300).

SECONDARY/METASTATIC TUMORS

Tumors metastatic to the vulva account for up to 8 percent of all tumors of the vulva (262,291). *Metastatic tumors* present at any site as a single or multiple, intradermal or subcutaneous mass. In some cases, vulvar ulcer or pain may be the initial presenting symptom (230). The metastases are usually present within the labia majora and in some cases, in the Bartholin gland (230,233,291). Half of the tumors metastasize from elsewhere in the genital tract; the remainder are from extragenital sites, with less than 10 percent having no identifiable primary tumor site (230). Metastatic tumor in the vulva was identified concurrently with the diagnosis of the primary tumor in 27 percent of the cases in one series (291), but it usually presents within 18 months of the initial diagnosis. The primary genital site is most commonly the cervix, followed by the endometrium, ovary, and vagina (291).

Metastatic squamous cell carcinomas from the cervix typically involve the dermal capillaries but not the overlying epithelium, whereas metastatic adenocarcinomas characteristically involve both the dermis and overlying epithelium and are often ulcerated (291). Metastasis from the bladder presents as a vulvar mass when the epidermis and underlying dermis is involved (233,235). Primary tumors at remote sites outside the genital tract, such as the breast, kidney (230,244,291), anus, rectum, colon, lung, pancreas (291), and stomach (5), also metastasize to the vulva. Malignant lymphoma, mycosis fungoides, gestational choriocarcinoma, malignant melanoma, and neuroblastoma have been reported to metastasize to the vulva (230,291,329). Of six cases of non-Hodgkin lymphoma in the vulva, four were metastatic and two arose as primary tumors (439).

Tumors also involve the vulva secondarily by direct extension from the vagina, urethra, urinary bladder, or rectum. Bladder and urethral tumors also spread within the epithelium and present as vulvar Paget disease of noncutaneous origin (461). Urethral carcinomas account for less than 1 percent of carcinomas involving the female genital tract and are usually encountered in elderly women (144). Most arise in the distal urethra and are squamous cell carcinomas, but some are transitional cell carcinomas (144,150,260). The survival rate for patients with urethral carcinoma is poor, between 22 and 27 percent, probably due to the rate of metastasis to the inguinal or pelvic nodes, which occurs in 20 to 50 percent of the cases (144,150,480).

Metastatic tumor involving the vulva is associated with a poor prognosis. In one series of 60 patients, 52 died of tumor, with a median survival of 7.5 months (range, 1 to 81 months) (230). Most patients are treated with radiation therapy and/or chemotherapy; radical operations are not indicated (230).

TUMOR-LIKE LESIONS

Pseudoepitheliomatous Hyperplasia

Pseudoepitheliomatous hyperplasia (PEH) is an epidermal reactive proliferative process that morphologically mimics squamous cell

carcinoma. PEH is identified in approximately 50 percent of cases of granular cell tumor of the vulva (471). It has also been associated with over 30 diseases that involve the skin (200).

Microscopically, PEH is characterized by a proliferation of squamous cells resulting in downgrowth by rete pegs into the underlying papillary dermis. The proliferating squamous cells have bland nuclei and sparse mitotic figures. Nonetheless, because of the marked downward growth of the rete pegs, sectioning shows irregularly shaped nests of epithelial cells in the dermis that can be confused with squamous cell carcinoma. It may not always be possible to distinguish PEH from squamous cell carcinoma if the biopsy does not demonstrate the underlying causative or associated process (471). Besides identifying the underlying process, additional findings that are of value in distinguishing PEH from squamous cell carcinoma are the absence of nuclear enlargement, pleomorphism, and hyperchromasia. Prominent enlarged nucleoli or abnormal mitotic figures are not present in PEH (471). PEH is confined to the papillary dermis and there is little, or no, cellular necrosis (200). These findings are not as reliable as the absence of nuclear atypia or the presence of an associated process, such as a granular cell tumor (471). An adequate deep biopsy is essential in establishing the diagnosis of PEH because it not only permits more thorough evaluation of the epithelial changes, but also reveals the underlying process responsible for the PEH.

Endometriosis and Decidua

Endometriosis of the vulva usually involves an episiotomy site or other area of trauma (200). It is most commonly found in the vestibule, presenting as a bluish to red cyst or nodule, or as a deep subcutaneous mass.

Vulvar endometrioma is a mass composed of benign endometrial glands and stroma, usually near the posterior fourchette. It may occur within an episiotomy scar. Cyclic changes in size related to the menstrual period may be noted by the patient.

Endometrial glands and stroma are present on microscopic examination in endometriosis (fig. 7-72) (200). A fibrotic or edematous dermal response may be noted. In some cases, a foreign body-giant cell reaction and hemosiderin-laden macrophages are seen, especially in cases in which surgery or episiotomy preceded the endometriosis.

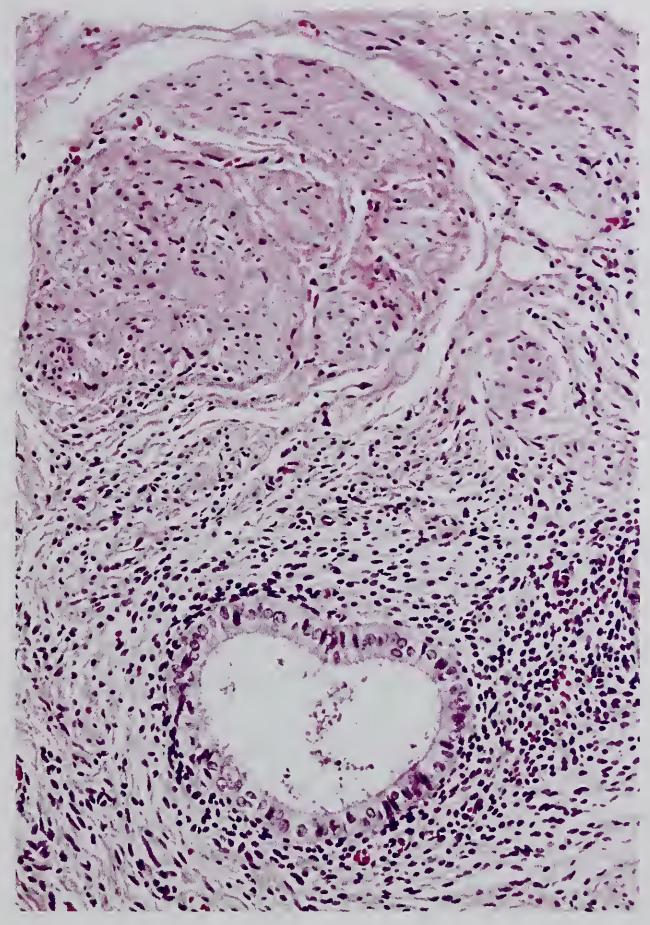


Figure 7-72

ENDOMETRIOSIS

An endometrial type gland is surrounded by characteristic endometrial stromal cells.

The presence of endometrial glands and stroma, or endometrial glands with surrounding hemofuscin or hemosiderin-laden macrophages and blood, is characteristic. In pregnancy or after progestin therapy, endometriosis may appear only as decidual tissue, with stromal cells containing pale amphophilic cytoplasm, sometimes associated with macrophages filled with altered blood pigment.

Clear cell adenocarcinoma has been described arising in vulvar endometriosis (30). A case of clear cell adenocarcinoma arose in endometriosis of the canal of Nuck adjacent to the right labium majus (269).

Vulvar endometrial stromal sarcoma has been reported arising in extraovarian endometriosis involving the canal of Nuck (182). Intratumoral

endometriosis of the vulva was associated with a composite tumor of dermatofibrosarcoma protuberans with giant cell fibroblastoma (207).

The differential diagnosis includes metastatic adenocarcinoma and hidradenoma, neither of which has endometrial stroma. The treatment of a localized endometrioma is local excision. Hormonal therapy is used in advanced cases.

Langerhans Cell Histiocytosis/ Granulomatosis (Histiocytosis X including Eosinophilic Granuloma)

Langerhans cell histiocytosis (*Langerhans granulomatosis*) includes three clinical forms: *Letterer-Siwe disease, Hand-Schüller-Christian disease* (the chronic progressive form), and *eosinophilic granuloma* (the benign localized form), which is the most common (338). Of 20 reported cases presenting as isolated lesions involving the vulva, 7 subsequently involved other sites (95,315,400,408,420).

Vulvar Langerhans cell histiocytosis presents as a pruritic, localized, cutaneous pigmented papule or nodule that measures 5 cm or larger in greatest dimension. The lesion may be ulcerated. On the vulva, the lesion occurs in patients from 2 to 91 years of age, although in other sites it occurs predominantly in children between 5 and 13 years of age (315,338,408). Systemic symptoms are rare but regional lymph nodes may be involved.

Microscopic examination reveals a localized dermal proliferation of histiocytes of Langerhans cell type with associated eosinophils, granulocytes, lymphocytes, and plasma cells. Foci of necrosis are surrounded by acute inflammatory infiltrates. The histiocytes are immunoreactive for S-100 protein and CD1A, and nonreactive for LCA, CD68, keratin, and vimentin. Electron microscopy demonstrates the diagnostic cytoplasmic Birbeck granules (315,338).

Benign Xanthogranuloma

Benign xanthogranuloma is generally classified within the nonhistiocytosis X group. It is a benign self-limited histiocytosis that is rare in the vulva. It is most common in infants or newborns in the juvenile form, however, adult xanthogranuloma involving the vulva is reported (59a). It is manifested in the genital area by multiple yellow to yellow-brown papules, plaques, or nodules. The eyes, as well as other cutaneous and visceral sites, may also be involved. In adults, xanthogranuloma may occur as a solitary lesion (59a).

The early lesions consist predominantly of histiocytes with little or no lipid. Older lesions are composed of histiocytes containing lipid intermixed with fibroblasts. Touton giant cells, foreign body giant cells, eosinophils, neutrophils, and plasma cells are usually present in mature lesions.

Verruciform Xanthoma

Verruciform xanthoma is a benign superficial, cutaneous and papillomatous lesion that has been rarely reported on the vulva in adult women (231,375). The xanthomas are single or multiple, and range in diameter from less than 2 mm to over 10 mm; a 15-mm periclitoral verruciform xanthoma has been reported (231). Verruciform xanthoma results from an accumulation of lipid-laden histiocytes within the papillary dermis, and is occasionally associated with hyperlipidemia. Because of its papular appearance, it may clinically be misinterpreted as condyloma acuminatum, carcinoma, or VIN (231,375). On microscopic examination, the epithelial surface is focally elevated, with some degree of acanthosis. The papillary dermis is filled with lipid-laden histiocytes (fig. 7-73).

Desmoid Tumor (Extraabdominal Fibromatosis/Aggressive Fibromatosis)

Desmoid tumor, also known as *extraabdominal fibromatosis* and *aggressive fibromatosis,* is a benign, locally infiltrative, fibromatous process originating in muscle-related connective tissue and adjacent fascia. It is rare in the vulva. It may rapidly enlarge in the pregnant patient (6,104,206,297). The peak age incidence is at 30 years. Localized pain is associated with advanced growth. Multiple desmoid tumors can involve more than one anatomic site.

The lesion is characterized by uniform cells that lack atypia and show no more than rare mitotic activity. A mitotic count of 1 per 10 high-power fields or more, with nuclear atypia and pleomorphism, suggests fibrosarcoma. Muscle involvement may result in atrophy; the atypical changes associated with atrophy of myocytes include nuclear pleomorphism.

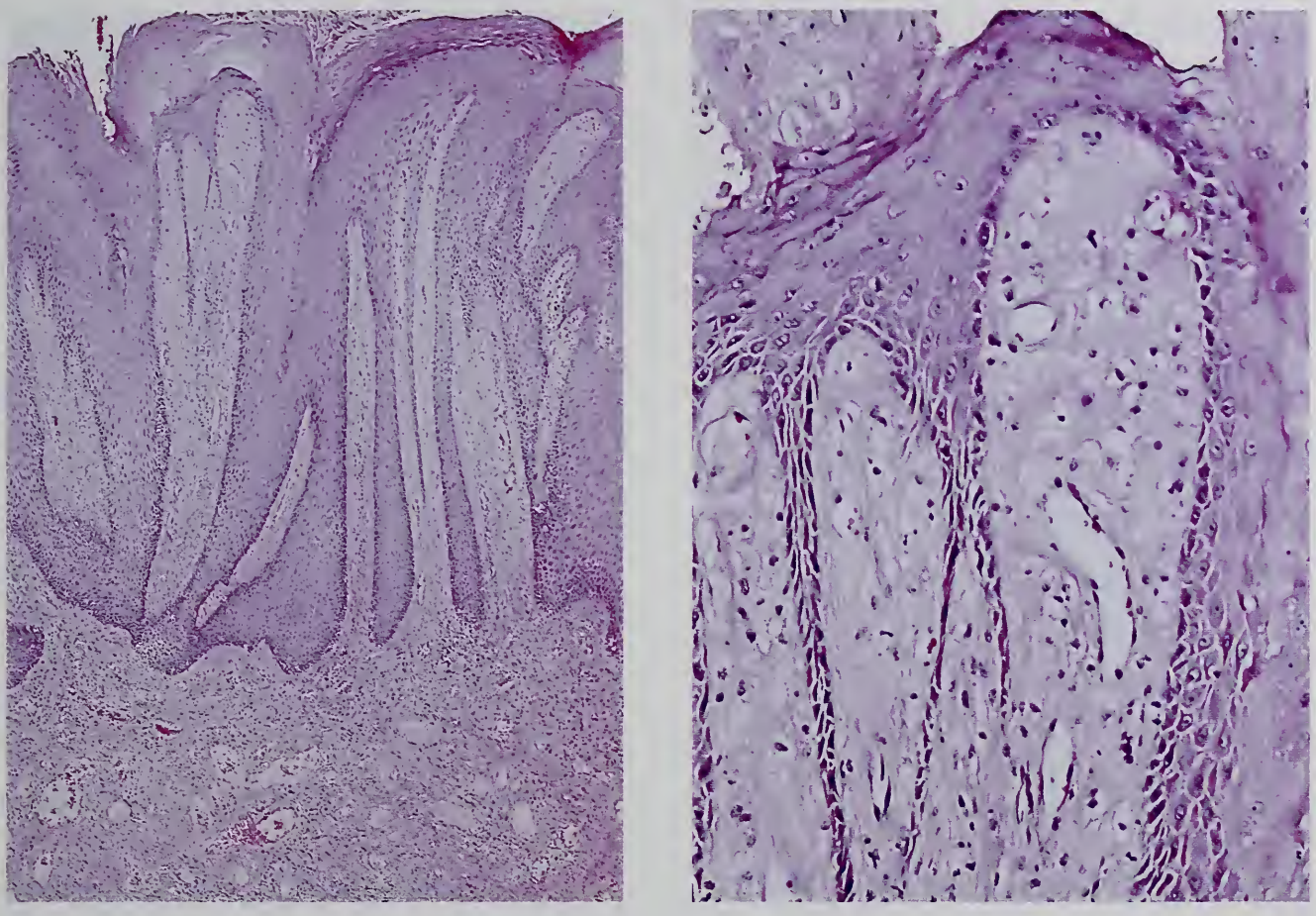


Figure 7-73

VERRUCIFORM XANTHOMA

Left: This papillomatous growth is characterized by prominent acanthotic epithelium. The cellular papillary dermis includes lipid-laden histiocytes. Hyperkeratosis is present

Right: Lipid-laden histiocytes are present within the papillary dermis.

Chronic inflammation, small hemorrhagic foci, and calcification may occur.

Sclerosing Lipogranuloma

Sclerosing lipogranuloma occurs generally secondary to the injection of oily material and may involve the external genitalia. In the vulva it presents as a discrete subcutaneous mass (309). On microscopic examination, the lesion is composed of globules of fat engulfed by histiocytes and multinucleated giant cells, with a variably hyalinized fibrous stroma. Regional lymph nodes may be enlarged and contain lipid-laden histiocytes.

Nodular Fasciitis (Pseudosarcomatous Fasciitis/Postoperative Fasciitis)

Nodular fasciitis is a benign tumor-like condition of myofibroblastic origin that is rare in the vulva. The lesion clinically presents as a solitary, subcutaneous soft tissue mass in the labium majus, and may be present for several years prior to diagnosis. The nodule may be painful (12,128,309). The lesion occurs in children as well as adults.

The mass of nodular fasciitis is usually under 4 cm in maximum dimension. It is firm and infiltrative, may involve muscle, and may appear contiguous with adjacent tissues, features suggesting malignancy.

Nodular fasciitis is localized in the subcutaneous tissue. Microscopically, the mass is hypercellular and composed of spindle-shaped fibroblasts and myofibroblasts; multinucleated giant cells may also be present (fig. 7-74). There may be some cellular atypia although significant nuclear pleomorphism is usually not present. The cells typically have uniform, large nuclei

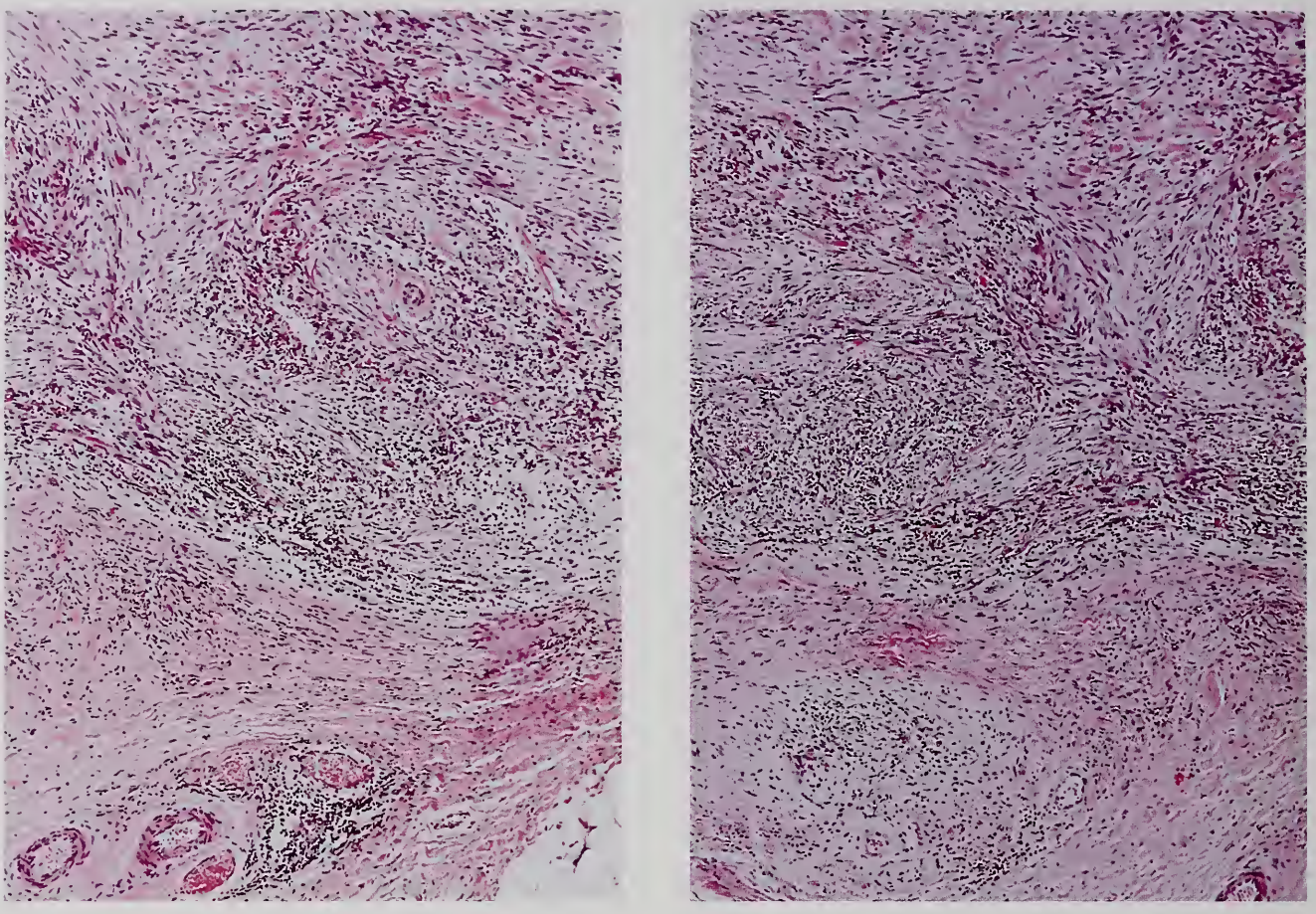


Figure 7-74

NODULAR FASCIITIS

Left: The lesion has irregular borders and a complex swirling pattern with variable cellularity. Myxoid change is seen in one area. Adjacent to the lesion is fibrous tissue containing small vessels.

Right: Spindle-shaped fibroblasts are arranged in a swirling pattern and form bands of collagen. (Left and right courtesy of Dr. Yao S. Fu, Los Angeles, CA.)

with vesicular chromatin and small nucleoli. The cytoplasm may be eosinophilic, and the cell borders are usually indistinct (275a). The nodule is typically highly vascular and small vessels, capillaries, and chronic inflammatory cells are often present. Areas of local collagenous or myxoid change may be observed. The mitotic count may be as high as 8 per 10 high-power fields, although abnormal mitoses are not seen (12,238,309). Entrapped epithelial elements and giant cells may be observed.

The spindle cells of nodular fasciitis are immunoreactive for vimentin, and usually express smooth muscle actin and muscle-specific actin. The multinucleated cells are immunoreactive for CD68. In one case, less than 5 percent of the cells were immunoreactive for MIB-1 (12). Immunohistochemical findings are typically negative for desmin, myoglobin (238), S-100 protein, and keratin.

Treatment is local excision (partial deep vulvectomy), which is diagnostic and therapeutic. Recurrences are treated by reexcision (309).

Postoperative Spindle Cell Nodule

Postoperative spindle cell nodule is a benign, superficial nodular proliferation that is more commonly associated with the urinary tract or vagina, but may present in the vulva. The mass usually presents within 3 months of surgery or injury, but in some cases there is no history of prior surgery or trauma. It is usually solitary and is present in the subcutaneous tissue. In some cases, it is polypoid or ulcerated (251,339,454).

The nodule is thought to arise from primitive progenitor cells of the submucosal or subcutaneous tissues, and not thought to be of myoepithelial origin.

On microscopic examination, the mass is located in the submucosa and is composed of spindle-shaped cells. Nuclear pleomorphism and hyperchromasia are usually not present. Mitotic figures are seen and are usually not atypical. Prominent blood vessels are present within the mass and inflammation may be present in and about the mass.

The differential diagnosis includes other spindle cell tumors including histiocytic tumors, leiomyoma, and neurofibroma and related tumors. Immunohistochemical studies are of value in distinguishing postoperative spindle cell nodules that typically do not express smooth muscle or neural markers, but do express bcl-2, CD34, and CD99 (454).

Crohn Disease

Crohn disease of the vulva is usually associated with a clinical history of typical Crohn disease. It has been reported in an adolescent (379). It may present as slit-like nonhealing ulcers that characteristically follow the natural folds of the skin, a fluctuant subcutaneous mass, apparent asymmetrical vulvar hypertrophy, or a polypoid mass (111,152,154,379). In addition to the vulva, the perineal, inguinal, and perianal areas may be involved. These ulcers may communicate with anal, rectal, and small intestinal fistulae. In some cases, vulvar ulcers precede the intestinal symptoms of Crohn disease or active Crohn disease (154).

Crohn disease is characterized histologically by a noncaseating granulomatous reaction without detectable causative organisms such as acid-fast bacilli, other bacteria, or fungi. Epithelial proliferation and polypoid mass formation may occur (154).

The treatment is highly variable and evidence-based trials may identify better treatments (154). Acquired lymphangioma is occasionally a late finding in vulvar Crohn disease (280).

Vulvitis Granulomatosa

Vulvitis granulomatosa is a non-necrotizing granulomatous inflammatory process of unknown etiology. It involves the vulva in preadolescents to the elderly. Clinically, there is symmetrical painless enlargement of the labia majora, and in some cases, the labia minora. In some cases, vulvar elephantiasis results. The condition appears similar to *cheilitis granulomatosa (Miescher-Melkersson-Rosenthal syndrome)*. Both of these conditions were observed in one patient (152). One case was associated with subsequent Crohn disease (152).

On microscopic examination, the inflammatory changes are similar to those found in Crohn disease. The dermal and submucosal tissues of the labia are edematous, with lymphangiectasia and fibrosis. A mononuclear cell infiltrate, which includes chronic inflammatory cells represented predominately by lymphocytes, with epithelioid histiocytes and histiocytic giant cells, accompanies the non-necrotizing granulomas.

The differential diagnosis of vulvitis granulomatosa includes conditions that obstruct lymphatic circulation and result in vulvar elephantiasis. These include congenital lymphatic hypoplasia, certain tumors including lymphangioma and metastatic tumors that involve regional lymphatics, postradiotherapy changes, and post-traumatic or surgical lymphedema as related to inguinal-femoral lymphadenectomy. Chronic stasis, such as confinement to a wheelchair, and chronic inflammatory noninfectious conditions, such as Crohn disease, may result in similar vulvar changes (152). Infectious diseases, including tuberculosis, granuloma inguinale, lymphogranuloma venereum, filariasis, and erysipelas, also cause such changes. Treatment must address the primary cause of the condition. Cosmetic or functional surgical excision may be needed in some cases.

CYSTS

Bartholin Duct Cyst

Bartholin duct cysts are caused by the obstruction of the duct of the gland resulting in distal distension of the duct. Most have a transitional-like epithelial lining, as seen in the normal Bartholin duct (fig. 7-75).

Mucinous Cyst

Mucinous cysts are typically found within the vestibule, and are solitary or multiple. Most arise from the minor vestibular glands.

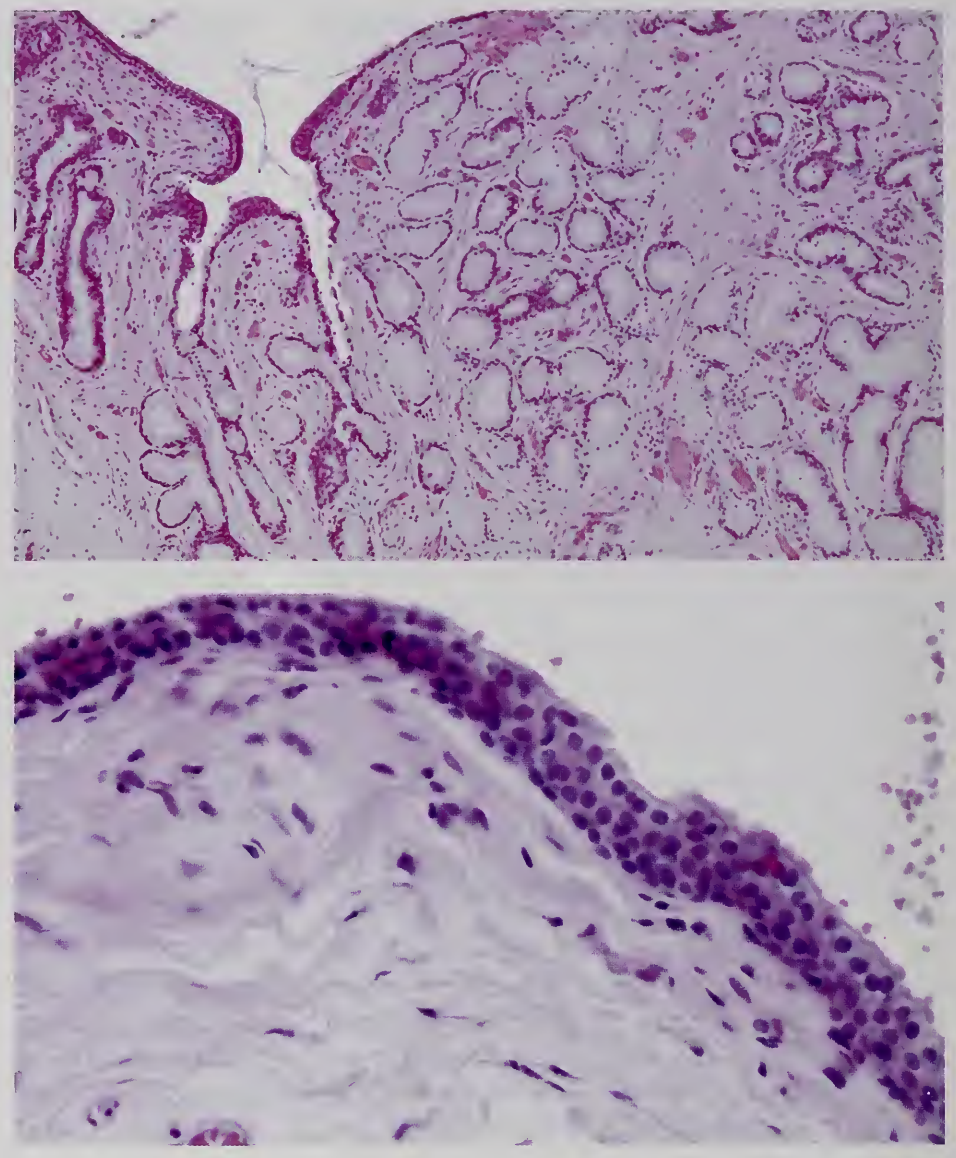


Figure 7-75

BARTHOLIN DUCT CYST

Top: The dilated Bartholin duct is contiguous with adjacent Bartholin gland minor ducts and acini.

Bottom: The cyst is lined by flattened transitional type epithelium.

The cyst is lined by mucinous epithelium that strongly stains with mucicarmine and Alcian blue. There may be focal squamous metaplasia of the cyst lining (fig. 7-76, top) (124,340). No myoepithelial cell layer or outer smooth muscle layer is present (124,360).

Acquired Mucinous Cysts/Mucinous Metaplasia

Acquired mucinous cysts (vulvar acquired adenosis)/mucinous metaplasia are lined by mucinous columnar epithelium or simple columnar epithelium. Mucinous metaplasia of the surface epithelium may be seen (fig. 7-76, bottom). They are described following 5-fluorouracil therapy of the vagina and vulvar vestibule for condyloma acuminatum (100,385). Excisional biopsy is therapeutic for mucinous cysts.

Epidermal Inclusion (Keratinous) Cyst

Epidermal inclusion cysts occur in infants, children, and adults. They are characteristically superficial, range in size from 2 to 5 mm, and involve the labia majora and the lateral portions of the labia minora. They are usually multiple (195). The clitoris may be distorted by such a cyst, resembling clitoral hypertrophy (237).

The cysts contain cheesy to grumous, yellow-white keratinous debris. They are lined by stratified squamous cornified epithelium, which has a granular layer and is immunoreactive for high molecular weight keratin (fig. 7-77). In some cases, the epithelial lining is markedly flattened. The cysts may be adjacent to sebaceous glands within the vulva. They do not require surgical

Figure 7-76

MUCOUS CYST/ MUCINOUS METAPLASIA

Top: The cyst, within the superficial submucosa, is lined by mucin-secreting columnar epithelial cells. The overlying epithelium is mildly hyperkeratotic.

Bottom: Submucosal cysts in the vulvar vestibule are lined by tall, pale, mucin-secreting columnar epithelial cells. Some chronic inflammatory cells are present. Some of the surface epithelium of the vestibule has mucinous columnar cells, characteristic of mucinous metaplasia.

excision unless there is secondary infection, rapid enlargement, or symptoms.

Mesonephric-Like Cyst

Since the mesonephric ducts do not descend to the vulvar anlage during embryologic development, these cysts are referred to as mesonephric-like. *Mesonephric-like cyst* is usually a solitary and superficial, blue-violet to dark red cystic mass, which is thin-walled and contains clear fluid. Microscopic examination reveals a single layer of low cuboidal to columnar nonciliated epithelium, which may be flattened as a result of the pressure of the cyst contents. A smooth muscle layer is characteristically present beneath the basement membrane of the epithelium. Surgical excision is therapeutic.

Ciliated Cyst

Ciliated cysts are rare in the vulva. The epithelial lining of the cyst consists of columnar cells, which include ciliated and secretory cells similar to those of tuboendometrial type epithelium. No muscle layer is present (fig. 7-78). The origin of the ciliated cyst is uncertain. Although it has been postulated that the cyst results from a developmental abnormality of the müllerian duct, there is no evidence that müllerian ducts contribute to the formation of the vulva (360). Ciliated columnar cells in vaginal and vulvar

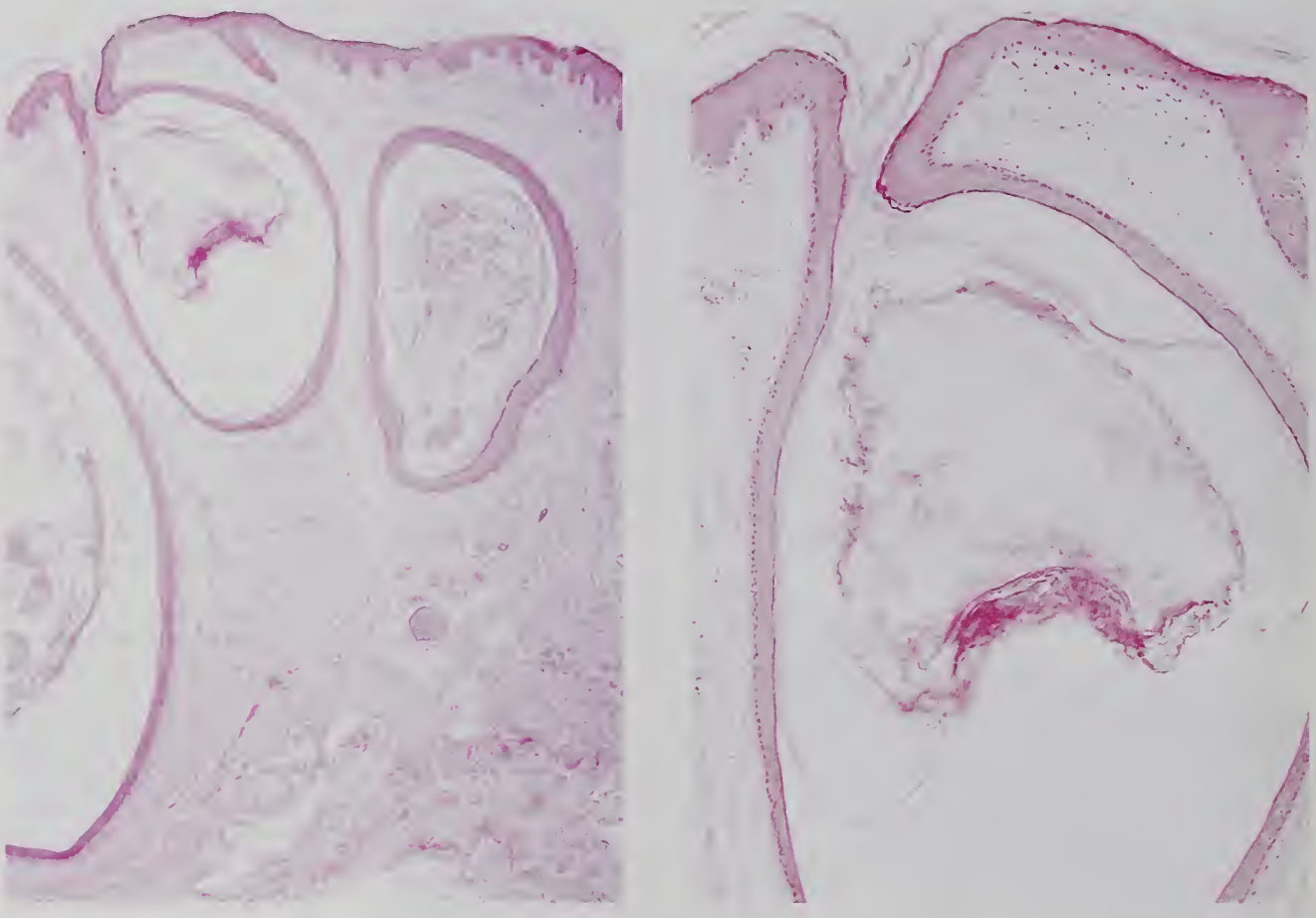


Figure 7-77

EPIDERMAL INCLUSION CYST

Left: The lining of the cyst is in continuity with the surface epithelium. The cyst lumen contains keratinous debis. Right: The epithelium lining is stratified squamous epithelium and the lumen contains keratinous debris.

epithelia have been observed following laser and 5-fluorouracil therapy (100,195,385). In one study, these changes were designated vulvar adenosis (385). Ciliated cysts are distinguished from endometriosis by the absence of endometrial stroma. Surgical excision is therapeutic.

Mesothelial Cyst (Cyst of the Canal of Nuck)

Mesothelial cyst, also known as *cyst of the canal of Nuck*, is typically located at the superolateral aspect of the labium majus at the level of the insertion of the round ligament. In approximately one third of the cases it is associated with an inguinal hernia. The cyst is thin walled and lined by flattened mesothelial cells. It varies in size and may exceed 5 cm in diameter. A large cyst may mimic an inguinal hernia clinically. Treatment is surgical excision.

Periurethral Cyst

Periurethral cysts are found just lateral to the urethral meatus. They are lined by transitional epithelium (fig. 7-79). They may arise from the ducts of Skene glands. Surgical excision is therapeutic.

OTHER EPITHELIAL DISORDERS OF SKIN AND MUCOSA

Lichen Sclerosus (Lichen Sclerosus et Atrophicus)

Definition. *Lichen sclerosus* is a dermatosis of unknown etiology characterized by progressive thinning of the epithelium, subepithelial edema with fibrin deposition, and an underlying zone of chronic inflammation within the dermis.

General Features. Lichen sclerosus is the most common dermatosis of the vulva. It occurs at any

age, but is most common in women of reproductive age or older. Children may experience dysuria, rectal bleeding, and pain with defecation related to perianal lichen sclerosus with anal fissures. In these children, anal and perianal ulcers must be differentiated from child abuse (270). The disease also affects the trunk and extremities when it involves the anogenital area. It may be limited to the vulva or involve the vulva and perianal area in a symmetric butterfly pattern.

Lichen sclerosus is sometimes associated with differentiated VIN and is associated with non-HPV–associated vulvar squamous cell carcinoma, a lesion observed primarily in older women. In over one third of the patients with vulvar invasive squamous cell carcinoma, lichen sclerosus is adjacent to the carcinoma (168,476,484). The frequency of squamous cell carcinoma arising in vulvar lichen sclerosus is from 3 to over 20 percent (56,384).

Gross Findings. The lesions are usually pale white, depigmented, flat plaque-like areas. In advanced cases, the skin has a wrinkled, parchment-like appearance. Areas of ecchymosis and excoriation, secondary to scratching, are often present. In severe cases, formation of bullae and ulceration are seen. With longstanding disease, shrinkage of the labia minora, majora, and frenulum may occur, associated with agglutination of the labia and stenosis of the vaginal introitus.

Microscopic Findings. Microscopic findings relate in part to the age of the lesion, location of

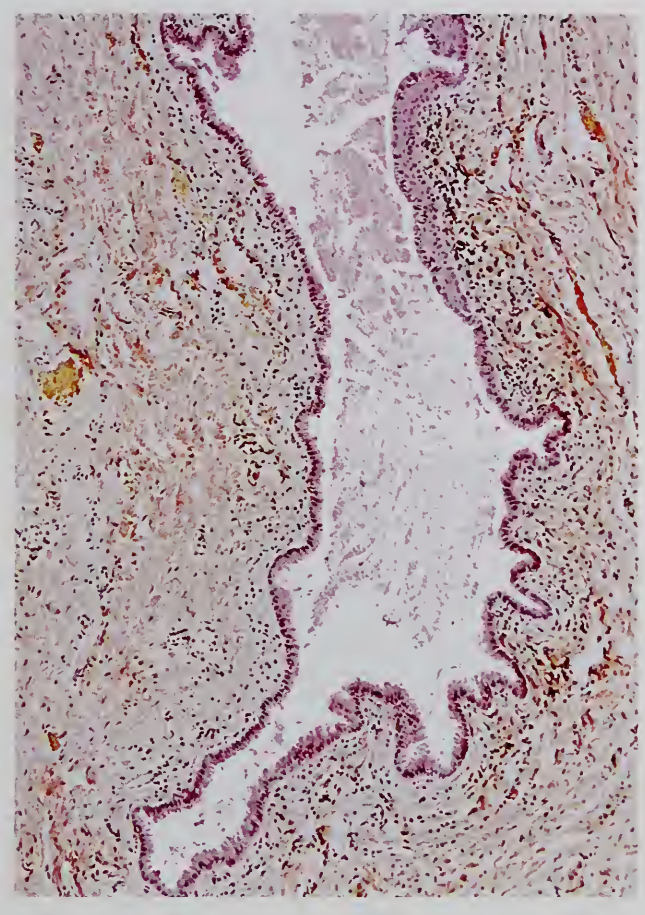


Figure 7-78

CILIATED CYST OF THE VULVAR VESTIBULE FOLLOWING 5-FLUOROURACIL THERAPY

This cyst contains ciliated cells and has some features of tubal-endometrial type epithelium; adjacent endometrial stroma is not identifiable, however.

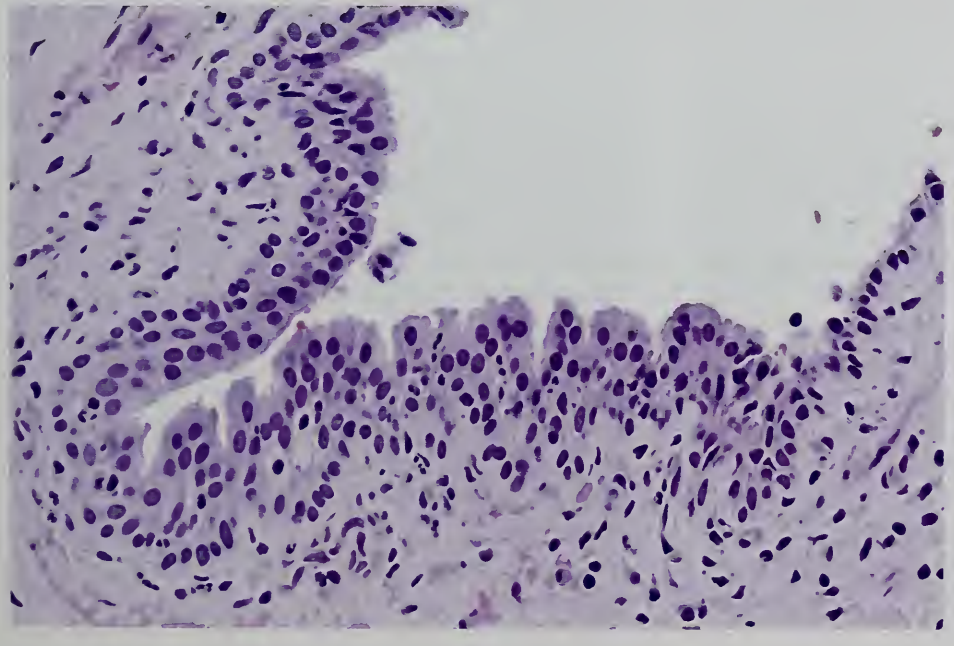


Figure 7-79

PERIURETHRAL CYST (SKENE GLAND CYST)

The cyst, lined by transitional type epithelium, lies immediately beneath the vestibular epithelium.

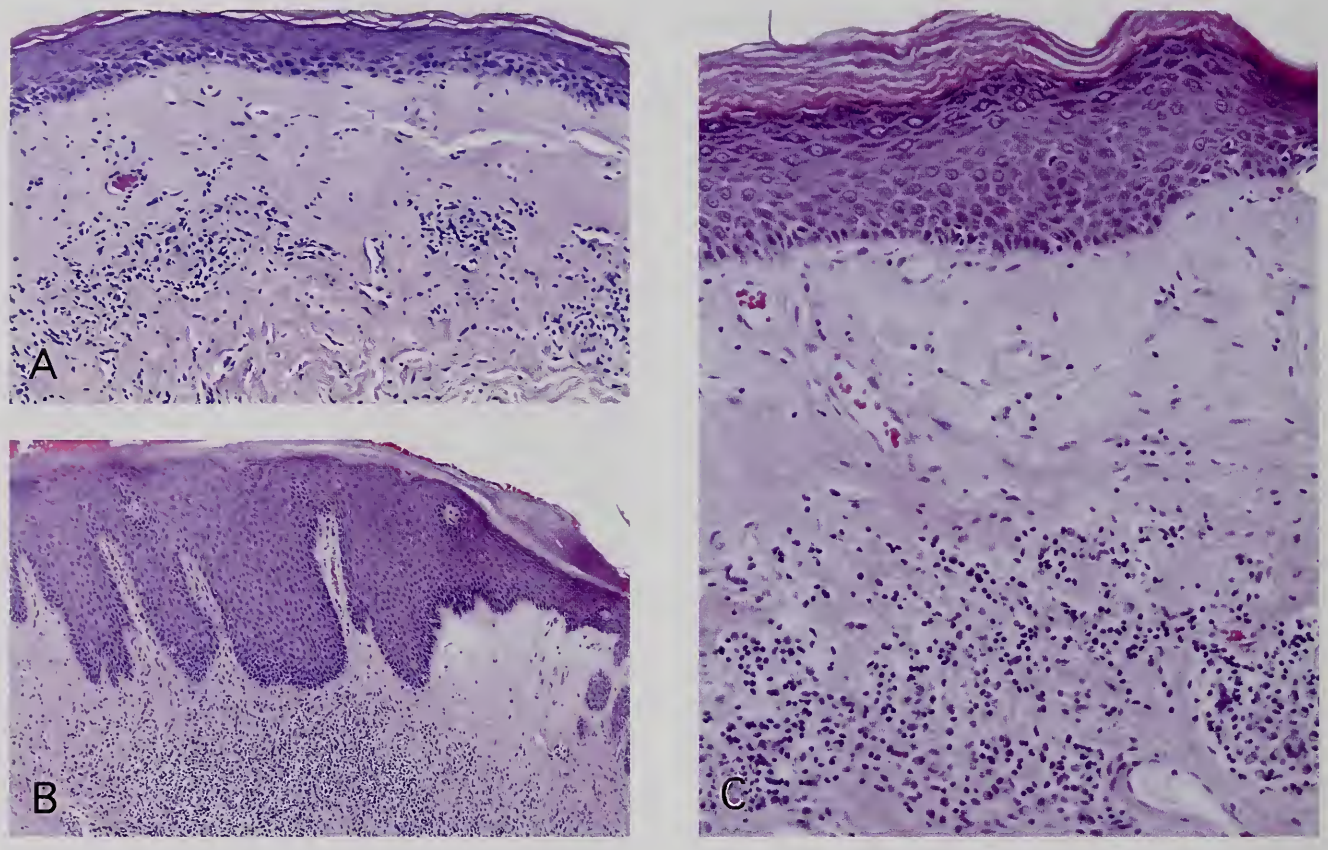


Figure 7-80

LICHEN SCLEROSUS

A: The epithelium is markedly thinned with a loss of rete ridges. Hyperkeratosis is present. Below the epithelium, the dermis is moderately edematous, fibrotic, and somewhat hypocellular. Deeper to this area, chronic inflammatory cells are seen above the more normal deeper dermis.

B: The markedly acanthotic squamous epithelium is immediately adjacent to thinned epithelium characteristic of lichen sclerosus. Superficial dermal changes of lichen sclerosus are present. Lichen sclerosus with lichen simplex chronicus is sometimes referred to as hyperplastic lichen sclerosus.

C: There is hyperkeratosis but the epithelium is thin. The subepithelial superficial dermis is edematous, fibrotic, and hypocellular, and contains a few small blood vessels. A moderate chronic inflammatory cell infiltrate is present in the dermis beneath the layer of fibrosis.

the lichen sclerosus on the vulva, and association with vulvar squamous cell carcinoma (56,383). Early lichen sclerosus is associated with patchy interface dermatitis and focal superficial fibrosis of the dermis immediately below the basement membrane of the overlying epithelium. In the middle stage of the disease, findings include epithelial thinning with loss of epithelial rete ridges, superficial subepithelial dermal fibrosis with dermal homogenization, and a predominantly lymphocytic infiltrate inferior to the dermal changes that may involve vessels (fig. 7-80). In the later stage, the subepithelial dermal fibrosis may be more marked, however, less inflammation is present. In all stages, there may be associated hyperkeratosis and excoriation with ulceration. The findings of thinning of the epithelium, subepithelial fibrosis, and loss of rete ridges become more pronounced as the disease progresses (56). The degree of hyperkeratosis and follicular plugging is highly variable, but may be marked.

Immediately beneath the epithelium, there is marked edema and fibrin deposition, and below the zone of edema there is an inflammatory infiltrate, which may be band-like and composed predominantly of lymphocytes accompanied by other chronic inflammatory cells. The epithelium separates from the basement membrane, resulting in focal subepithelial vacuolar

change. This is a useful feature in the distinction of lichen sclerosus from localized scleroderma (321). In severe cases, the subepithelial vacuolar change progresses to the formation of bullae. Extravasated blood within the superficial dermis is a common finding. Lichen sclerosus may be associated with lichen simplex chronicus; when this occurs, both diagnoses should be given.

Immunohistochemical Findings. Assessment of epithelial cell proliferation using Ki-67 has demonstrated little epithelial immunoreactivity in the usual lichen sclerosus; reactivity is increased in the epithelial cells of lichen sclerosus associated with vulvar squamous cell carcinoma (384). In the inflammatory dermal infiltrate of lichen sclerosus, T cells significantly outnumber B cells. In this lymphocyte-rich inflammatory infiltrate, the killer T cells significantly outnumber helper T cells (23). Fibrin is detected within the subepithelial dermis with the use of immunofluorescence techniques (51). Complement (C3) and immunoglobulin (Ig)M are also present within this edematous area (51, 94,119). The presence of these substances may reflect reactive rather than primary accumulation because they are found within areas of superficial trauma in otherwise normal skin. Retinoic acid receptors have been studied in lichen sclerosus and there appears to be loss of these receptors (27). Immunohistochemistry is not helpful diagnostically.

Differential Diagnosis. The differential diagnosis includes lichen planus and morphea. In one of its phases, lichen planus has a distinctive lichenoid chronic inflammatory infiltrate that involves the basal layer of the epithelium, adjacent superficial dermis, and preserved rete ridges. The prominent dermal edema of lichen sclerosus is not present. Morphea is characterized by epithelial thinning, loss of rete ridges, and collagenization of the dermis. The collagenization is deeper than seen in lichen sclerosus and may extend around the eccrine gland ducts. The subepithelial edema of lichen sclerosus is typically absent in morphea. A deep inflammatory cell infiltrate may be seen in both processes. In lichen sclerosus, however, it is more band-like and not localized to the advancing edge of the lesion, as seen in the early phases of morphea. Vascular changes, including perivascular lymphocytic infiltrates and subsequent fibrosis, are characteristic of morphea but absent in lichen sclerosus (321).

Treatment and Prognosis. There is no completely effective treatment for lichen sclerosus. The most commonly used therapy in adults is the topical administration of a high potency corticosteroid, such as clobetasol propionate 0.05 percent, which is effective with long-term use (86).

The lifetime risk of women with vulvar lichen sclerosus developing squamous cell carcinoma is unknown but appears to be greater than 3 percent (56,168). In children with vulvar lichen sclerosus, some regression of symptoms and physical findings may occur with menarche, however, the lichen sclerosus usually persists and will eventually lead to more advanced changes, including introital stenosis, if not clinically managed.

Lichen Simplex Chronicus (Formerly Squamous Cell Hyperplasia/ Hyperplastic Dystrophy)

Lichen simplex chronicus is a term used to describe an epithelial disorder characterized by acanthosis and variable hyperkeratosis without atypia, significant associated inflammation, or evidence of a specific dermatosis. It now includes the term *squamous cell hyperplasia* (242a).

This lesion is a common disorder thought to be secondary to local irritation, including chronic scratching. Although often clinically diagnosed, it is not biopsied as often as lichen sclerosus. Lichen simplex chronicus is not considered a precursor to vulvar carcinoma nor is it considered a risk for carcinoma as is lichen sclerosus. It may, however, be observed adjacent to vulvar differentiated VIN or squamous carcinoma in some cases.

Lichen simplex chronicus usually appears as a discrete white lesion, reflecting the presence of epithelial thickening and edema or hyperkeratosis. The lesion is plaque-like and seldom extensive. A dark red to violet color may be observed if the hyperkeratosis and edema are lacking or if scratching causes areas of excoriation. Unlike lichen sclerosus, lichen simpex chronicus is rarely symmetric. Fissures may form, especially when the lesion involves the fourchette or perineal body.

The epithelium is hyperplastic with prominent acanthosis (fig. 7-81). Hyperkeratosis

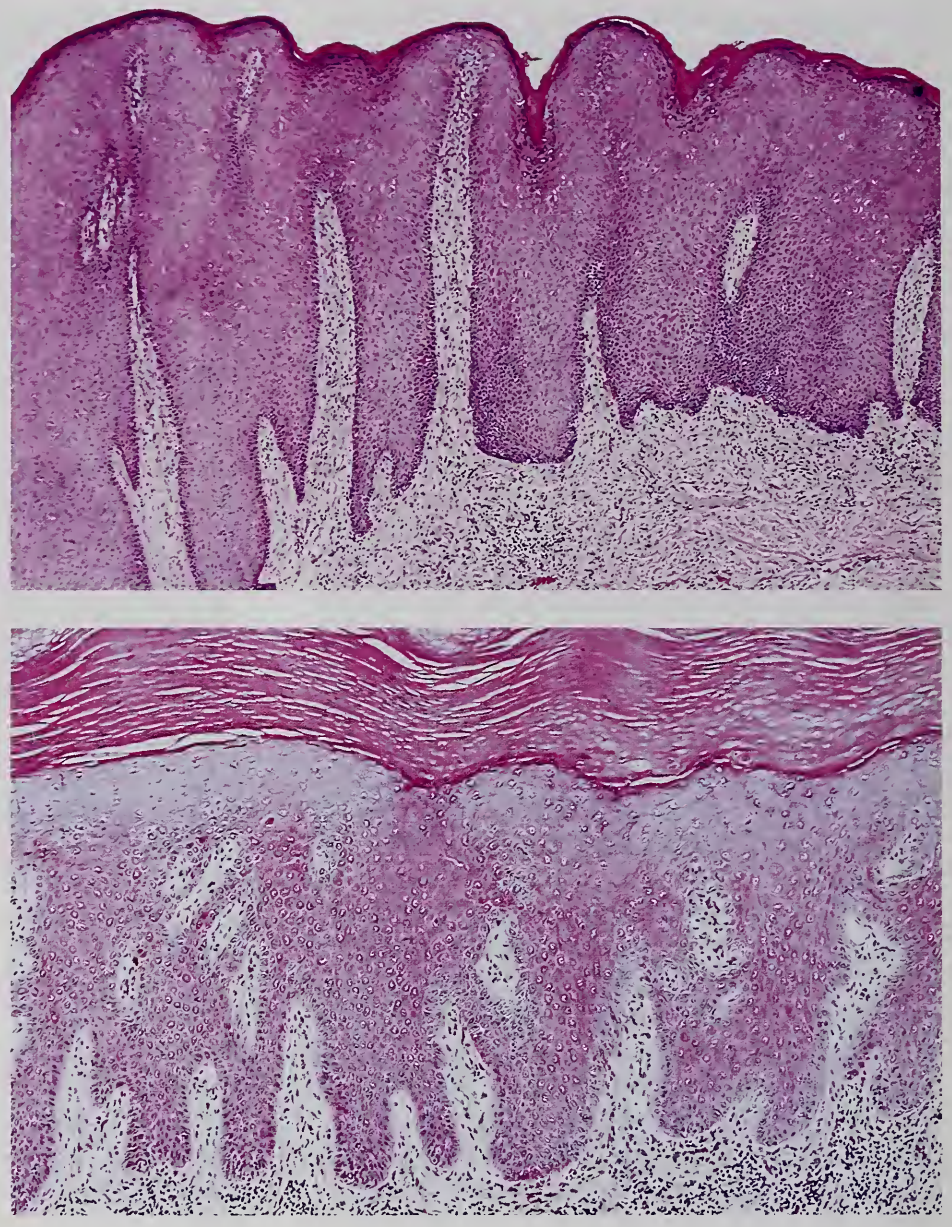


Figure 7-81

LICHEN SIMPLEX CHRONICUS

Top: Prominent acanthosis and thickening of the epithelium with slight hyperkeratosis and spongiosis are present. There is no atypia. There is mild chronic inflammation in the dermis.

Bottom: The epithelium is thickened and shows surface maturation. The hyperkeratosis and the chronic inflammation in the dermis are mild.

and parakeratosis are usually present and epithelial edema (spongiosis) may be present. The epithelial cells are mature and there is no nuclear atypia. Abnormal mitotic figures are not present. Mild to moderate dermal inflammation may be seen, but is not conspicuous unless there is associated excoriation or infection. Multiple biopsies are recommended to exclude foci of VIN. Should lichen sclerosus be found in the adjacent epithelium, the diagnosis should be lichen sclerosus with adjacent lichen simplex chronicus instead of mixed dystrophy (359).

The differential diagnosis includes changes secondary to fungal infection or HPV infection. If evidence of either of these infections is found, lichen simplex chronicus should not be diagnosed. Lichen simplex chronicus may have prominent acanthosis, with marked elongation and widening of the rete ridges. Hyperkeratosis and parakeratosis may be found in both. The inflammation may be perivascular and extend into the epidermis (exocytosis). In addition, dense collagenization of the dermis immediately beneath the epidermal-dermal junction may be seen. White sponge nevus has been described on the vulva and, although rare, is another entity in the differential diagnosis (46).

Local contact irritant factors or associated vaginitis exacerbate the lesion and should also

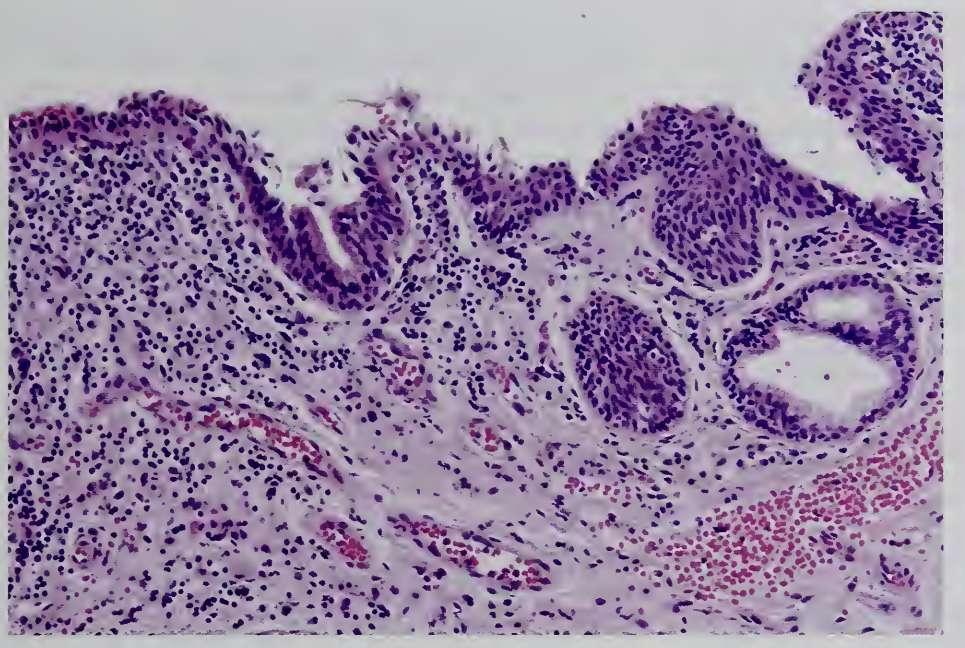


Figure 7-82

IDIOPATHIC CHRONIC INFLAMMATION OF THE VULVAR VESTIBULE

There is mucosal erosion with loss of glycogen-rich epithelium. Mucin-secreting columnar epithelial cells are present in one area (columnar cell metaplasia). In the submucosa, a small mucous cyst is associated with a moderate superficial submucosal chronic inflammatory infiltrate.

be treated. The prognosis is usually good and most patients respond within 1 month to topical corticosteroid treatment.

Inflammation of the Vulvar Vestibule of Unknown Etiology: Vulvar Vestibulitis and Vulvodynia

The clinical causes of vulvar vestibular pain are currently referred to as *vulvodynia* by the International Society for the Study of Vulvovaginal Disease (ISSVD). There is considerable controversy regarding the use of the term *vestibulitis* and the ISSVD has proposed that the term not be used clinically due to the lack of well-defined criteria (161). The clinical and pathologic findings included here define vulvar vestibulitis as an inflammatory condition of the vulvar vestibule of uncertain orgin associated with external dyspareunia, inflammation within the vestibule, and point tenderness of the inflamed areas. The inflammation presents as multiple erythematous foci of inflammation within the vestibule, localized to or associated with one or more minor vestibular glands and, occasionally, Bartholin duct openings (123). This excludes other cases of vulvar vestibular pain not associated with inflammation or other known causes of vulvar inflammation.

Microscopically, vulvar vestibulitis consists of a superficial submucosal, lymphocytic inflammatory infiltrate consisting predominantly of lymphocytes with some plasma cells and neutrophils, or occasional eosinophils (fig. 7-82) (340). Significant inflammation must be present, recognizing that some inflammation is normally seen in vestibular epithelium removed in normal asymptomatic women undergoing vaginal reparative procedures. Some epithelial erosion and occasional superficial ulceration may also be present.

The cause of vulvar vestibulitis is unknown; however, impairment in the downregulation of interleukin-1-beta activity by interleukin-1 receptor antagonist is reported in some women with vulvar vestibulitis (132). HPV infection is not as common in these patients as compared to normal controls (255,464).

No entirely effective therapy has been reported, however, oral antifungal therapy and biofeedback therapy are of value in some patients. Partial or total superficial vulvar vestibulectomy has been performed, but no well-controlled studies exist to support surgery as the primary preferred treatment. Symptoms and findings may recur, even with surgical excisional procedures. Surgical excision is usually reserved for refractory cases when medical therapy and management has not relieved the pain. Dietary changes, such as low oxylate diets, have not proven effective (161,253).

Other Dermatoses

Inflammatory dermatoses that involve the vulva generally have histologic features that do not differ significantly from those seen

on nongenital skin. Among such disorders are included *cicatricial* and *bullous pemphigoid* (108,256,431), *lichen planus* (236), *vulvo-vaginal-gingival syndrome* (323), *papular acantholytic dyskeratosis of vulva* (69,228), *plasma cell vulvitis* (*vulvitis circumscripta plasmacellularis*), *Fox-Fordyce disease*, and *hidradenitis suppurativa* (283,468).

This is a partial list of reported conditions. The reader is referred to appropriate textbooks and references for descriptions of these lesions.

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